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EXPERIMENTAL EDEMA (NEPHROSIS) IN DOGS IN RELATION TO EDEMA OF RENAL ORIGIN IN PATIENTS *

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For many years a keen interest and much controversy have developed over the views of von Müller,[1] Munk,[2] Volnard and Fahr [3] and Epstein,[4] concerning the condition that they have termed nephrosis.

For the past two years we have had the opportunity to study the cases of nephritis with edema in the wards and at the renal clinic of the Peter Bent Brigham Hospital in Boston. Most of these cases have shown fairly constant and comparable conditions generally regarded as typical of nephrosis. They were characterized by oliguria, albuminuria, relatively noncellular urine sediment, edema, normal renal function as measured by several tests, usually normal blood pressure, a lowered metabolism and a chemical blood picture, which consisted of low serum protein, reversed albumin-globulin ratio, increased blood cholesterol, phosphorus and fibrinogen and a decreased blood calcium.

During the course of our study in the renal clinic, three cases were observed which were unusual and, to us, of particular interest. All three patients had had acute nephritis which apparently had subsided except for the continued loss of a large amount (from 6 to 15 Gm. per day) of albumin in the urine. All were on a restricted protein intake. Studies of the blood showed a gradual fall in the serum proteins, and later the appearance of edema, together with all of the observations regarded as characteristic of nephrosis. We were impressed by the

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3. Volhard, Franz, and Fahr, T.: Die Brightsche Nierenkrankheit, Berlin, Julius Springer, 1914.

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constant association of this well marked albuminuria with the characteristic blood serum picture. We noticed that the greater the albuminuria, the lower was the serum protein, and the lower the serum protein, especially the albumin fraction, the greater was the edema. This led us to wonder whether the whole symptom-complex of nephrosis might not be secondary to the low serum protein. In order to determine this point, we have attempted to produce in dogs a serum picture analogous to that found in these patients. As a result the following procedure was devised.

METHOD

Four young adult dogs were selected and kept under observation during a control period varying from one to six weeks. During this period the animals were trained so that all of the procedures could be done readily on them without the use of any form of anesthetic, narcotic or sedative. Plasmapheresis[5] was the method of choice to produce a low proteinemia. The dogs were bled at intervals varying from four to sixty-eight days and in total amounts varying from 3,750 cc. to 42,500 cc. The blood was centrifugated, the serum discarded and the cells reinfused mixed with Locke's solution. One liter of warm saline was given by stomach tube a short time before the operation to prevent shock. The bleeding was done by puncture of the femoral arteries, and reinfusion was done into any available vein. All procedures were done with strictly aseptic technic, and at no time was there any evidence of any form of infection, except for a slight infection in dog 1 following nephrectomy.

The total serum protein, serum albumin and serum globulin determinations were done by the combined methods of Howe,[6] Wu,[7] and Kock and McMeekin,[8] as described by Hawk and Bergeim;[9] blood cholesterol as described by Bloor, Pelkan, and Allen;[10] blood phosphorus by the method of Fiske and Subbarow;[11] blood calcium by the method of Clark and Collip;[12] fibrinogen by the method

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of Foster and Whipple;[13] blood volume by the method suggested by Keith, Rowntree, and Geraghty[14] with the modification of Murphy, Monroe, and Fitz;[15] cell volume by the method of Haden.[16] The basal metabolism was done with the Benedict-Roth machine, by means of the Blalock mask;[17] the cardiac output according to the Fick principle[18] and the oxygen and carbon dioxide content of the arterial and the venous blood, drawn directly from the right and left sides of the heart, were done with the manometric apparatus of Van Slyke and Neill.[19]

PROTOCOL

Dog 1 was a male shepherd that weighed 19.2 Kg. Observations on this animal may conveniently be divided into four periods: (1) preliminary control period of one month; (2) first period of plasmapheresis up to nephrectomy (ninety-two days); (3) period of convalescence, one month during which there was no plasmapheresis and (4) second period of plasmapheresis of twenty-four days.

In the control period urinalysis, blood pressure, urea nitrogen of the blood and phthalein tests were normal. The cholesterol was considered above the normal of from 80 to 100 mg. per hundred cubic centimeters. The serum albumin fraction was slightly below normal (table 1).

Plasmapheresis was then begun and continued at varying intervals over a period of ninety-two days up to the time at which nephrectomy was done. The daily amount of blood removed ranged from a minimum of 400 cc. to a maximum of 1,500 cc. The total amount of blood removed during this period was 18,000 cc. On the thirty-eighth day edema of the extremities occurred, and was maintained irregularly during this second period. The edema varied from slight pitting of the extremities to generalized anasarca. The weight increased as edema accumulated. The greatest increase was 2.7 Kg. During the experimental period, weakness and muscular wasting with a decrease in weight of 1.2 Kg. during the edema-free stages were noted. On the forty-third day, albumin, hyaline and granular casts appeared in the urine. During this second period the cholesterol rose to as high as 254 mg. per hundred cubic centimeters. The blood calcium dropped to 9.09 mg., and the phosphorus increased to 15 mg. per hundred cubic centimeters. The red blood count decreased to 4,100,000. The cell content of the blood measured by the hematocrit decreased to 21.85 per cent. No changes occurred in the blood pressure or renal function test. There was only a slight increase of the fibrinogen. The basal metabolic rate decreased from 156 to 112

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TABLE 1.—*Summary of Observations on Dog 1**

Date	Wt.	Art. Sect.	Urine	B.P.	P.S.P.	B.U.N.	Chol.	Ca	P	Fib.	R.B.C.	Hem.	T.P.	Alb.	Glob.	B.M.R.	Card.O.	Bl.Vol.	Ed.	Leg Meas.	Comment
10/25/28	....	...	1.040; negative	110/ 70	55	13	170	10.09	....	...	8.1	41•	6.02	2.52	3.50	194	.....	.....	.....	...	Control period; animal's condition good
11/27/28	19.2	450	.....	110/ 70	..	..	174	.....	....	...	...	....	6.82	2.48	4.34	...	.....	.....	.....	...	Plasmapheresis started
11/28/28	....	450	.....	110/ 60	..	21	254	.....	4.36	0.6	5.3	....	5.34	0.72	4.62	...	.....	.....	.....	...	
11/30/28	18.6	450	.....	110/ 60	..	..	...	.....	....	...	6.1	41.7	6.37	2.49	3.88	...	.....	.....	.....	...	
12/ 4/29	18.0	450	.....	.....	..	..	...	.....	4.16	...	6.1	41.0	5.56	1.26	4.30	...	.....	.....	.....	...	
12/ 6/28	17.6	0	Negative	130/ 80	..	22	164	.....	4.2	...	...	....	....	....	....	190	.....	.....	.....	...	
12/10/28	....	450	.....	.....	..	17	184	.....	4.3	...	...	....	4.29	1.61	2.68	...	.....	.....	.....	...	
12/11/28	....	...	.....	138/ 80	..	..	...	.....	....	...	5.6	32	4.68	1.63	3.05	...	.....	.....	.....	...	
12/14/28	....	450	Negative	.....	..	..	...	.....	....	...	...	....	4.67	1.12	3.55	...	.....	.....	.....	...	
12/16/28	18.0	700	Negative	.....	..	15	...	9.09	2.6	...	5.3	....	5.07	1.20	3.87	...	.....	.....	.....	...	
12/18/28	....	700	.....	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	.....	...	
12/20/20	19.0	700	.....	.....	..	..	...	.....	....	...	...	....	....	....	....	150	.....	.....	+	..	
12/26/28	19.0	700	Negative	.....	..	17	100	9.34	....	...	...	....	5.10	0.67	4.43	142	.....	.....	+	...	
12/28/28	18.9	700	.....	.....	..	..	...	.....	....	...	...	....	...	....	....	163	.....	.....	0	...	
1/ 2/29	18.4	700	Negative	140/ 60	..	14	125	9.54	....	...	...	21.8	4.03	0.63	3.40	...	.....	.....	++	...	
1/ 3/29	18.7	700	.....	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	++	...	
1/ 4/29	20.2	700	Negative	12!/ 60	..	..	...	.....	....	...	...	....	4.02	0.64	3.38	127	.....	.....	+++	...	
1/ 5/29	....	0	.....	122/ 60	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	++	..	
1/ 7/29	19.2	750	Negative	.....	..	10	...	.....	....	0.3	...	....	4.38	0.81	3.57	156	.....	.....	0	...	
1/ 8/29	19.6	750	.....	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	+	...	
1/ 9/29	....	750	.....	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	++	..	
1/10/29	20.0	750	.....	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	++	...	
1/11/29	20.3	750	Negative	.....	..	..	...	.....	....	...	...	....	4.08	0.60	3.48	...	.....	.....	++±	...	
1/12/29	20.4	750	.....	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	+++	...	
1/13/29	20.0	0	.....	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	+	4.2	
1/14/29	19.2	750	Alb. 0; casts +	.....	..	..	...	.....	12	...	...	....	4.79	0.83	3.86	...	.....	.....	0	3.2	
1/15/29	19.3	900	.....	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	+	3.7	
1/16/29	19.4	0	Alb. 0; casts +	.....	..	..	...	.....	....	...	...	....	....	....	....	147	.....	.....	0	3.2	
1/18/29	19.2	0	Alb. 0; casts +	.....	..	..	105	10.65	12	...	...	27.0	4.35	0.82	3.53	138	.....	1,384	0	...	
1/24/29	19.1	0	.....	13 / 80	..	..	...	.....	....	...	...	....	....	....	....	132	1,720	.....	0	...	
1/28/29	19.2	0	.....	.....	..	..	...	.....	....	...	...	....	....	....	....	125	1,739	1,552	0	...	
1/29/29	19.3	900, 600	Alb. 0; casts +	.....	..	..	...	.....	....	...	...	....	5.13	0.97	4.26	...	.....	.....	0	3.2	
1/30/29	20.6	900	Alb. +; casts +	.....	..	..	120	10.46	15	...	4.1	36.4	....	....	....	...	.....	.....	++	4.0	
1/31/29	20.4	900, 500	Alb. +; casts +	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	++±	4.7	Edema of body wall ?; ascites

2/ 1/29	21.9	400	Alb. +; casts +	.....	50	..	60	9.24	12	...	4.9	20.4	3.55	0.6	2.95	...	.....	1,554	++++	...	Generalized edema; ascites; slightly dyspneic
2/ 2/29	21.3	0	Alb. +	.....	..	..	...	.....	....	...	...	....	....	....	....	112	3,930	.....	++++	5.0	Nephrectomy (right kidney)
2/ 5/29	18.2	0	Casts +	.....	..	.	...	.....	18	...	...	....	4.87	0.83	4.04	135	.....	.....	0	3.2	Convalescent period
2/ 9/29	....	0	Alb. +; casts +	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	.....	...	Slight superficial infection of wound
2/13/29	....	700	.....	.....	..	..	206	11.57	17	0.95	...	....	6.55	2.41	4.14	...	.....	.....	0	...	
2/22/29	17.6	0	Fat; casts	152/ 60	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	0	...	Wound healed; clean
3/ 5/29	17.3	450	Alb.; fat; casts	.....	..	..	130	10.74	12	...	...	....	4.91	2.03	2.88	...	.....	.....	0	3.5	Second perold of plasmapheresis
3/ 6/29	17.5	450	.....	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	0	...	
3/ 7/29	17.6	600	Negative	160/ 76	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	0	...	
3/ 8/29	17.6	450	.....	.....	..	..	120	9.7	13	...	...	....	4.41	1.76	2.65	...	.....	.....	±	3.7	
3/ 9/29	17.6	0	Alb.; casts	160/ 70	54	..	...	.....	....	...	6.2	29.0	....	....	....	...	.....	.....	0	...	
3/11/29	17.6	550	Alb.; casts	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	0	...	
3/12/29	17.4	450, 450	Alb.; casts	.....	..	11	132	.....	....	...	...	....	4.89	1.57	3.31	...	.....	.....	0	3.5	
3/13/29	....	450	Alb.; casts	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	+	3.7	Edema of legs and chest wall
3/14/29	17.6	450	Alb.; sp.gr. 1.010	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	++	4.0	
3/15/29	17.7	550	Alb.; casts	.....	..	..	120	12.0	15	...	6.1	30	3.60	1.39	2.21	...	.....	.....	+	3.7	
3/18/29	17.1	600	.....	.....	..	..	196	10.65	5	1.1	...	....	3.95	1.82	2.13	...	.....	.....	0	3.2	Partial collapse
3/19/29	18.2	450	Casts	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	0	...	
3/20/29	17.2	450	Alb.	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	0	...	
3/21/29	17.5	450	Alb.; casts	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	0	3.2	Not responding to plasmapheresis
3/22/29	17.4	450	.....	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	0	...	
3/25/29	17.4	400, 400	.....	.....	..	8	...	9.71	4	...	...	....	4.88	1.64	3.24	...	.....	.....	0	...	
3/26/29	18.3	450, 450	Negative; 1.010	220/100	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	0	...	
3/27/29	19.1	450	Negative; 1.010	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	... .	+	...	
3/28/29	17.9	450	Alb.; casts	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	0	...	
3/29/29	17.4	450	Alb.; casts	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	0	...	Animal killed (ether, 10 cc. intracardiac)

* The following explanatory terms are for all tables: Wt., weight in kilograms; Art. Sect., number of cubic centimeters of blood removed from femoral artery; B.P., blood pressure in millimeters of mercury; P.S.P., the phenolsulphonphthalein test for kidney function; Cho., milligrams of cholesterol per hundred cubic centimeters of blood; Ca, milligrams of calcium per hundred cubic centimeters of blood; P, milligrams of phosphorus per hundred cubic centimeters of blood; Fib., grams of fibrinogen per hundred cubic centimeters of blood serum; R.B.C., red blood cell count; Hem., hematocrit, percentage of red blood cells; T.P., grams of serum protein per hundred cubic centimeters of blood; Alb., grams of serum albumin per hundred cubic centimeters of blood; Glob., grams of serum globulin per hundred cubic centimeters; B.M.R., basal metabolic rate, calories per kilogram hour; Card.O., cardiac output, number of cubic centimeters of blood per minute; Bl.Vol., blood volume in cubic centimeters; Ed., edema; Leg Meas., circumference of hind legs in inches.

calories per kilogram hour at the time that there was generalized edema. The cardiac output increased to 3,930 cc. per minute, while the blood volume remained constant.

At the end of this period a right-sided nephrectomy was done, and the dog was allowed to convalesce for one month, during which time plasmapheresis was omitted. (The specimen of the organs of this as well as of all the other animals was placed immediately after nephrectomy and death in fixatives of formaldehyde, Zenkers and Kaiserling's solution). There were 480 cc. of a clear, straw-colored fluid in the abdominal cavity. The right kidney was normal in size and appearance. The cortex and medulla measured 11 and 14 mm. in thickness, respectively. The capsule stripped easily and the surface appeared normal. On the cut surfaces grayish-yellow, bulging bands extending through the cortex were noted. Microscopically, the predominating lesion was a moderate degree of swelling of the tubules which in numerous instances were markedly damaged. Isolated tubules showing almost complete disintegration of the epithelium could be followed for considerable distance. In rare instances hyaline droplets were found in tubular epithelium and within the lumina of the tubules. There were also rare but definite areas of plasma cell infiltration in the cortical tubular region. A rare glomerulus showed hyalinization of Bowman's capsule. Appropriate stains brought out considerable fatty infiltration along the basement membrane of the tubules (fig. 8).

Plasmapheresis was resumed on dog 1 after one month of convalescence, and was continued for twenty-four days. At the beginning of this third period the dog weighed 17.3 Kg. The blood removed per day was a minimum of 450 cc. and a maximum of 900 cc.; the total amount removed was 10,400 cc. On the fourth day slight edema of the extremities occurred, but could not be maintained. The last nine days the dog was edema-free except for the twenty-second day when edema of the chest wall and neck region occurred. This disappeared on the following day and did not reform, although plasmapheresis was continued for two days more. The weight remained constant except for the twenty-second day when it increased to 19.1 Kg. Urinalyses showed that the specific gravity of the urine had fallen from 1.040 to 1.010. Albumin, hyaline and granular casts, fat droplets, small renal cells and occasionally slight traces of sugar were found. The blood pressure rose to 220 systolic and 100 diastolic. The urea nitrogen of the blood and phthalein tests remained normal. The blood cholesterol increased to 196 mg. The blood phosphorus rose to 15 mg.; but by the end of the experiment it had returned to a normal level of 4 mg. per hundred cubic centimeters. The fibrinogen rose to 1.1 Gm. per hundred cubic centimeters of serum. No remarkable change occurred in the calcium. The red blood cell count remained at the normal level of 6,240,000. The cell content of the blood as measured by the hematocrit was 29 per cent. At the end of this period the dog was killed and autopsy was performed. The left kidney weighed 57 Gm. The cortex and medulla measured 11 and 13 mm. in thickness, respectively. This kidney differed little in gross appearance and size from the right one, although the capsule was somewhat thicker. The cut surface showed the same grayish brown streaks, slightly more prominent than before, radiating through the cortical region to the surface. Microscopically, however, there was a marked difference in the two kidneys. The predominating lesion, as in the first kidney removed, was in the tubules. Swelling and tubular atrophy were marked. There were numerous areas of lymphoid and plasma cell infiltration and connective tissue replacement throughout the cortical tubular region. Many glomeruli showed thickening and hyalinization of the capsule with more glomerular atrophy than was seen previ-

ously. Special stains revealed rather marked fatty infiltration or degeneration of the tubules, and most of the glomeruli and capsules, too, showed fatty infitration (fig. 9).

Dog 2 was a large male shepherd weighing 21 Kg. The preliminary control period was one week. All control studies were normal (table 2).

Plasmapheresis was then begun and continued at varying intervals for four months, with removal of a minimum of 450 and a maximum of 1,800 cc. per day, or a total of 42,500 cc. On the fifth day after plasmapheresis was begun, slight pitting edema of the legs was noted. As plasmapheresis was continued, generalized anasarca was observed. The edema varied in amount and time of occurrence, depending on the amount and frequency of plasmapheresis. During the last eighteen days the edema was maintained and was marked, but the amount and frequency of plasmapheresis had to be markedly increased. The weight during the period of marked edema increased to 25.8 Kg. During the edema-free periods the dog showed weakness and muscular wasting. On the thirty-second day after plasmapheresis, albumin, hyaline and granular casts, fat droplets, renal cells and occasional red blood cells were noted in the urine. After the third month of plasmapheresis, the specific gravity of the urine dropped to 1.010. Slight traces of sugar were found in the urine occasionally. The blood pressure gradually rose to 170 and 190 systolic, and to 90 and 110 diastolic, but was not constant. The urea nitrogen of the blood and results of the phthalein tests remained normal. The blood cholesterol increased to 180 and 216 mg. The blood calcium decreased to 8.22 mg. The blood phosphorus rose to 17 mg., and the fibrinogen rose to 1.4 Gm. per hundred cubic centimeters of serum. The red blood cells decreased to 3,350,000. The hematocrit, cell content of the blood, dropped to 20.1 per cent. The basal metabolic rate showed a decrease to as low as 123 calories per kilogram hour during the edematous stages. The cardiac output increased during the period of marked edema to as high as 7,820 cc. per minute. No remarkable change occurred in the blood volume. At the end of the fourth month, the dog was killed for pathologic study. The right kidney weighed 66 Gm. and the left 62 Gm. The cortex and medulla were 10 and 14 mm. in thickness, respectively. Grossly, the kidneys showed slightly thickened capsules which stripped with a little more difficulty in comparison with the others. The surface of the kidneys showed small white patches which formed scattered depressions on the surface. The cut surface showed an area of marked scar formation which appeared to be 3 or 4 mm. in thickness throughout the tubular region. From this diffuse scar area there were bands radiating through the cortex which caused the dimpling and scarring of the surface already described. Between these bands were yellow colored patches which proved to be fat. Microscopically, the tubules showed marked cloudy swelling with desquamation of the epithelium and marked tubular atrophy. In the tubules, hyaline and fatty casts were noted. There were linear areas of marked lymphoid and plasma cell infiltration accompanying the area of scar tissue replacement throughout the tubular region. Where these areas of connective tissue and small round cell infiltration encircled the glomeruli, the latter were atrophied and showed marked thickening of the capsule (fig. 10). Specially stained frozen sections showed some fatty infiltration of the tubules, but was not so marked as that observed in dogs 1 and 4.

Dog 3 was a large male shepherd that weighed 23 Kg. The preliminary control period was six weeks. During this time studies were repeatedly made as described previously. Results of urinalyses, blood pressure readings, renal function tests, and blood studies were normal. At the end of this period, plasmapheresis was done on four successive days, with removal of a minimum of 675

TABLE 2.—*Summary of Observations on Dog 2*

Date	Wt.	Art. Sect.	Urine	B.P.	P.S.P.	B.U.N.	Chol.	Ca	P	Fib.	R.B.C.	Hem.	T.P.	Alb.	Glob.	B.M.R.	Card.O.	Bl.Vol.	Ed.	Leg Meas.	Comment
12/ 6/28	....	...	Negative	138/ 80	60	22	100	10.20	....	1.3	5.4	31.6	....	....	....	...	.....	.....	.....	...	Control period
12/10/28	21.0	...	Negative	156/ 80	..	..	...	.....	4	...	...	....	5.96	2.00	3.96	...	.....	.....	.....	...	Condition good
12/13/28	....	...	Sp. gr. 1.040	.....	..	15	...	.....	....	...	...	....	6.02	2.04	3.88	...	.....	.....	.....	...	
12/14/28	21.8	450	Negative	.....	..	..	...	.....	....	1.4	...	36.8	....	....	....	...	.....	.....	.....	...	Plasmapheresis
12/15/28	....	450	.....	.....	..	..	...	.....	....	...	...	....	4.67	0.94	3.93	...	.....	.....	.....	...	
12/16/28	....	450	Negative	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	.....	...	
12/18/28	22.8	750	Negative	.....	..	15	90	.....	9.6	...	...	....	4.59	0.90	3.64	...	.....	.....	.....	...	
12/20/28	22.2	...	.....	.....	..	..	...	.....	....	...	..	....	....	....	....	166	.....	.....	+	...	
12/22/28	22.3	750	.....	.....	..	..	...	.....	....	...	...	....	....	....	....	164	.....	.....	0	...	
12/26/28	20.8	750	Negative	.....	..	15	95	9.90	8.9	...	...	....	5.40	0.86	4.54	...	.....	.....	0	...	
12/28/28	20.8	750	Negatvie	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	0	...	
12/31/28	20.0	750	.....	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	0	...	
1/ 1/29	20.4	750	Sp. gr. 1.042	100/110	..	15	116	9.14	....	...	5.4	30.0	4.65	0.98	3.67	...	.....	.....	+	...	Edema of extremitis
1/ 3/29	20.4	750	.....	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	++	...	
1/ 4/29	21.0	750	.....	.....	..	..	...	.....	....	...	...	....	3.91	0.70	3.21	...	.....	.....	++	...	
1/ 7/29	21.0	750	.....	158/ 90	..	13	...	.....	....	0.55	...	....	4.88	0.55	4.32	...	.....	.....	+++	...	Generalized edema
1/ 8/29	21.2	750	.....	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	+++	...	
1/ 9/29	....	750	.....	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	++	...	
1/10/29	21.0	750	Negative	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	+	...	
1/11/29	21.2	750	.....	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	++	...	
1/12/29	21.6	750	.....	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	++	...	
1/14/29	20.1	750	.....	.....	..	..	...	.....	14	...	...	....	5.00	0.90	4.10	...	.....	.....	0	3.3	
1/15/29	21.3	900	.....	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	+	3.7	
1/16/29	20.5	0	Negative	.....	..	..	...	.....	....	...	...	....	....	....	....	145	.....	.....	0	....	
1/17/29	20.5	...	Casts	.....	..	..	...	.....	....	...	...	....	....	....	....	134	2,250	1,900	0	3.3	
1/21/29	20.6	...	.....	.....	..	..	106	10.65	14	0.3	...	24	4.69	0.83	3.86	137	2,200	2,042	0	...	
1/22/29	22.0	900, 900	Casts	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	0	3.3	
1/23/29	23.6	900, 900	.....	.....	..	..	...	.....	....	...	...	....	2.75	0.50	2.25	...	.....	.....	+	3.5	
1/24/29	23.4	900	.....	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	++	4.2	
1/25/29	22.3	900	.....	160/ 80	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	++	4.5	
1/27/29	22.4	0	.....	.....	..	..	...	.....	....	1.2	...	....	....	....	....	134	3,900	2,040	+++	5.0	Ascites
1/28/29	21.4	900	.....	.....	..	..	...	.....	....	...	...	.....	....	....	....	...	.....	.....	0	...	
1/29/29	21.6	900	Casts	.....	..	..	60	9.34	17	0.8	...	.....	3.29	0.74	2.55	...	.....	.....	±	3.7	
1/30/29	22.6	900	Alb. +; casts +	.....	..	..	...	9.15	....	...	...	....	....	....	....	...	.....	.....	+	3.7	
1/31/29	22.9	900	Alb. +; casts +	.....	..	..	...	.....	....	...	3.8	17.7	....	....	....	...	.....	.....	.....	...	
2/ 1/29	23.6	900	Alb. 0; casts +	.....	..	11	80	9.15	13	...	...	.....	2.82	0.41	2.41	...	.....	.....	++	4.2	
2/ 5/29	21.6	0	Alb. +; casts +	.....	..	..	216	10.64	....	...	...	.....	5.26	0.95	4.31	127	2,920	2,266	0	3.5	

2/ 7/29	21.2	900	Alb. +; casts +	.....	..	..	213	10.18	15	0.4	...	....	5.34	0.90	4.44	...	.....	.....	0	...		
2/13/29	....	700	.....	.....	..	..	190	9.81	19	0.5	...	....	5.13	2.06	3.07	...	.....	.....	0	...		
2/18/29	....	675	Alb. +; casts +	.....	..	13	189	10.81	16	...	...	....	4.56	2.09	2.47	...	.....	.....	0	...		
2/21/29	22.3	900	Alb. +; casts +	190/110	..	..	100	9.78	12	...	4.0	23.3	3.17	1.57	1.60	157	2,790	.....	0	...		
2/23/29	21.6	0	.....	190/120	..	8	100	4.71	13	...	...	....	3.57	1.87	1.70	193	2,700	.....	0	...		
2/25/29	22.6	700	.....	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	0	...		
2/26/29	22.4	900	Casts +; fat +	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	0	...		
2/27/29	23.1	900	.....	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	0	...		
2/28/29	....	900, 900	Casts +	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	0	...		
3/ 1/29	24.5	900	Casts +	.....	..	10	115	8.22	10	...	...	....	1.90	0.58	1.32	...	.....	.....	+	3.7		
3/ 2/29	24.1	0	Negative	.....	..	..	...	.....	....	0.5	5.3	28	....	....	....	151	6,220	1,759	++	4.0		
3/ 4/29	24.1	900	.....	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	0	...		
3/ 5/29	24.1	900	.....	.....	..	10	...	9.15	14	...	...	....	3.33	1.49	1.84	...	.....	.....	0	...		
3/ 6/29	23.8	900	Casts +	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	++	4.5		
3/ 7/29	23.6	900	Alb. +; casts	144/ 70	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	+++	5.5		
3/ 8/29	23.8	900	.....	.....	..	..	111	9.34	13	...	...	....	2.95	1.12	1.83	...	.....	.....	+++	5.0		
3/ 9/29	24.3	0	.....	150/ 90	35	..	...	.....	....	...	4.4	27.7	....	....	....	146	3,870	1,659	+++	4.5		
3/11/29	24.2	900	Negative; 1.010	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	0	...		
3/12/29	24.2	675, 900	Casts +	.....	..	10	116	.....	....	...	...	....	3.36	1.24	2.02	...	.....	.....	+	3.8		
3/13/29	24.8	900	Casts +	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	+++	4.5		
3/14/29	25.0	900	.....	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	+++	4.0		
3/15/29	25.0	900	Casts +	.....	..	..	100	11.20	17	...	...	....	2.60	0.69	1.91	...	.....	.....	++++	5.5	Marked edema; ascites	
3/16/29	24.6	0	.....	.....	..	..	...	.....	....	...	3.3	19.6	....	....	....	164	7,150	2,487	++++	5.7		
3/18/29	22.1	850	.....	.....	..	..	188	10.65	5	...	...	....	3.08	1.41	1.67	...	.....	.....	0	3.7		
3/19/29	23.7	900	Alb. +; casts +	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	+±	4.2		
3/20/29	23.7	900	.....	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	+±	4.2		
3/21/29	23.8	900	Negative	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	++	...		
3/22/29	24.0	900	Sp. gr. 1.010	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	++	...		
3/25/29	22.0	900, 900	.....	.....	..	10	...	9.53	4	...	...	....	3.97	1.26	2.71	...	.....	.....	0	3.7		
3/26/29	23.6	900, 900	Casts +; fat +	168/ 90	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	+	...		
3/27/29	25.1	900	.....	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	++++	5.0	Marked edema; ascites	
3/28/29	24.9	900	Alb. +; casts +	.....	..	..	80	6.6	....	1.1	...	....	2.80	0.63	2.17	...	.....	.....	++++	5.7		
3/29/29	24.4	900	Casts +; fat +	.....	..	..	...	.....	....	...	...	20.4	....	....	....	...	.....	.....	++++	5.1		
3/30/29	25.2	900	Alb. +; casts +	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	++++	5.0	Generalized anasarca	
3/31/29	24.2	900	.....	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	+++	4.0		
4/ 1/29	24.2	700, 700	Casts +; fat +	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	++	...		
4/ 2/29	24.6	800, 800	Alb. +	.....	..	..	...	.....	....	...	...	....	....	....	....	...	.....	.....	+++	...		
4/ 3/29	25.8	900	Alb. +; fat +	.....	..	10	...	9.62	....	...	3.3	20.1	2.76	0.85	1.91	123	7,820	2,320	++++	...	Animal killed (ether, 10 cc. intracardiac)	

cc. and a maximum of 1,500 cc. of blood per day, or a total of 3,720 cc. At the end of this time, a well marked edema of the extremities and scrotum appeared. Albumin, hyaline and granular casts were found in the urine. No changes occurred in the blood studies (table 3). The dog died suddenly due to collapse.

The kidneys of this dog illustrate our earliest stage in the progressive kidney lesion observed in this series of animals. The kidneys weighed 60 Gm., the cortex 9 mm. and the medulla 15 mm. Grossly, there was no variation from the normal. Microscopically, the tubules showed cloudy swelling with slight desquamation of the epithelium in the convoluted portions. The glomeruli were normal except for a precipitate (possible albumin) seen in the capsular spaces, streaming down into the tubules (fig. 11).

Dog 4 was a male bull that weighed 15 Kg. The preliminary control period was two weeks. Urinalyses, blood pressure, phthalein test, blood studies, basal metabolism, cardiac output, and blood volume were all normal. Plasmapheresis was then begun and continued for ten days with removal of a minimum of 200 cc. and a maximum of 900 cc. of blood per day, or a total of 4,925 cc. On the third day edema occurred, and this was maintained for two weeks. The maximum weight was 15.9 Kg. on the twelfth day, and the minimum 12.7 Kg. on the eighteenth day after plasmapheresis was begun. Slight muscular wasting and loss of strength was observed during the experiment. On the seventh day of plasmapheresis, albumin, hyaline casts, fat droplets and renal cells appeared in the urine. No changes were observed in the blood pressure, renal function test, cholesterol or fibrinogen. The blood calcium decreased to 8.9 mg., and the blood phosphorus rose to 12 mg. per hundred cubic centimeters. The red blood count dropped to 4,690,000, and the cell content of the blood as measured by the hematocrit, to 26.3 per cent. The total serum protein, serum albumin and serum globulin dropped to as low as 3.06, 1.02 and 2.04 mg. per hundred cubic centimeters, respectively. The metabolic rate decreased to 193 calories per kilogram hour, but returned to normal by the end of the rest period. The cardiac output increased to as high as 4,070 cc. per minute, while the blood volume remained at the normal level (table 4).

One month after discontinuing the plasmapheresis, the animal was killed, and an autopsy was performed to determine whether kidney repair had taken place. The right kidney weighed 56 Gm., the left 59 Gm., the cortex 9 mm., and the medulla 15 mm. Grossly, the kidneys were normal in size and appearance. The cut surface revealed grayish-brown streaks radiating out toward the capsule. Microscopically, cloudy swelling and some hyaline droplet formation with desquamation of the epithelium and extrusion of the nuclei were observed in the convoluted portions. The tubules contained occasional hyaline and fatty casts. Scattered at infrequent intervals were areas of small round cell and plasma cell infiltration. Occasionally, a glomerulus showed marked atrophy, hyalinization and thickening of the capsule, while many of the others showed apparent enlargement of the capillary tufts. Special fat stain revealed marked fatty infiltration of the tubules and occasionally of the glomeruli (figs. 12 and 13). Many of the tubules appeared normal. Occasional mitotic figures possibly indicating regeneration were found in the tubular epithelium.

Studies of the other tissues of these dogs, such as thyroid, heart, liver, spleen, adrenals, etc., showed no abnormalities except for a possible increase of the connective tissue in the spleen and liver of dogs 1 and 2. All of the dogs except dog 1 were killed immediately by the injection of 10 cc. of ether, directly into the heart.

TABLE 3.—*Summary of Observations on Dog 3*

Date	Wt.	Art. Sect.	Urine	B.P.	P.S.P.	B.U.N.	Chol.	Ca	P	Fib.	R.B.C.	Hem.	T.P.	Alb.	Glob.	B.M.R.	Card.O.	Bl.Vol.	Ed.	Leg Meas.	Comment
1/ 9/29	23.0	...	Negative	130/ 70	14	55	...	.....	..	..	...	....	5.82	1.75	4.17	...	.....	.....	.....	3.5	Condition fair; nutrition poor
1/12/29	23.6	...	Negative	.....	..	..	...	.....	..	..	...	....	....	....	....	106	.....	.....	.....	...	
1/17/29	23.8	...	Negative	.....	..	..	...	.....	..	..	...	26.4	....	....	....	158.6	.....	1,674	.....	...	
1/21/29	23.7	...	.....	.....	..	..	74	.....	18	..	...	22.0	5.26	1.18	4.08	183	.....	2,755	.....	3.5	Bronchitis; coughing
1/23/29	23.6	...	.....	.....	..	..	...	.....	..	..	3.8	20.0	....	....	....	...	.....	2,100	.....	...	Anemic; condition poor
1/25/29	....	...	.....	.....	..	..	...	11.30	19	..	...	....	6.34	1.23	5.11	...	.....	.....	.....	...	
2/ 5/29	23.0	...	Negative	.....	..	..	100	11.07	..	..	5.4	....	6.56	2.32	4.24	...	.....	.....	.....	...	
2/ 8/29	23.5	...	.....	.....	..	..	...	.....	..	..	...	....	....	....	....	171	2,600	2,441	.....	...	Condition improving
2/11/29	22.3	...	Negative	.....	10	..	...	.....	..	..	5.8	26.3	....	....	....	190	.....	2,485	.....	...	
2/15/29	22.3	...	.....	.....	..	..	...	.....	..	..	...	....	....	....	....	227	8,550	.....	.....	...	
2/16/29	....	...	Negative	.....	..	..	...	.....	..	..	...	....	....	....	....	228	7,870	.....	.....	...	Shown only for pathologic study
2/18/29	22.3	675	Negative	.....	..	..	...	.....	..	..	...	....	....	....	....	...	.....	.....	.....	...	Symptoms of hemorrhage
2/19/29	....	700, 800	Negative	.....	..	..	...	.....	..	..	...	....	....	....	....	...	.....	.....	.....	3.5	Partial shock
2/20/29	....	800	Alb. 0; casts +	.....	..	..	...	.....	..	..	...	....	....	....	....	...	.....	.....	++	3.75	
2/21/29	22.5	800	Alb.; casts	.....	..	..	60	10.65	11	..	6.4	23.2	5.07	2.98	2.00	...	.....	.....	++	4.12	Sudden collapse

TABLE 4.—*Summary of Observations on Dog 4*

Date	Wt.	Art. Sect.	Urine	B.P.	P.S.P.	B.U.N.	Chol.	Ca	P	Fib.	R.B.C.	Hem.	T.P.	Alb.	Glob.	B.M.R.	Card.O.	Bl.Vol.	Ed.	Leg Meas.	Comment
2/ 7/29	15.4	...	Negative	120/ 80	..	13	129	9.62	4	....	...	....	6.78	2.29	3.49	...	.....	.....	.....	...	General condition good
2/22/29	15.4	...	.....	.....	55	..	...	.....	....	.....	...	....	....	....	....	245	.....	.....	.....	...	
2/23/29	14.2	...	.....	.....	..	..	...	.....	....	....	6.8	35.4	....	....	....	250	2,400	1,644	.....	3.25	
2/25/29	15.1	450	Negative	140/ 78	..	8	40	11.13	12	0.65	...	....	6.51	2.72	3.79	...	.....	.....	.....	...	Plasmapheresis
2/26/29	15.2	675	.....	.....	..	..	...	.....	....	....	...	....	....	....	....	...	2,580	.....	.....	...	Dyspneic
2/27/29	15.3	450, 450	Negative	.....	..	..	...	.....	....	....	...	....	....	....	....	...	.....	.....	.....	±	3.36	Pitting of ankles
2/28/29	14.0	450	.....	.....	..	..	112	9.15	8.5	....	5.3	25.8	3.06	1.02	2.04	...	.....	.....	±±	4.0	Edema of legs, prepuce and scrotum
3/ 1/29	14.6	600	.....	.....	..	..	...	.....	....	....	...	....	....	....	....	...	.....	.....	++	4.5	
3/ 2/29	14.6	0	.....	.....	..	..	...	.....	....	0.45	...	....	....	....	....	229	4,070	1,511	++	...	
3/ 4/29	....	400	Alb. +; casts	.....	..	..	...	.....	....	....	...	....	....	....	....	...	.....	.....	±	...	
3/ 5/29	....	400	.....	.....	..	10	...	8.97	12	....	...	....	3.56	1.04	2.52	...	.....	.....	++	4.2	
3/ 6/29	14.5	400	Negative	.....	..	..	...	.....	....	....	...	....	....	....	....	212	.....	.....	+++±	4.7	
3/ 7/29	14.6	200	Alb. 0; casts	142/ 70	..	..	...	.....	....	....	...	....	....	....	....	...	.....	.....	+++±	...	
3/ 8/29	14.7	450	.....	.....	..	..	111	10.37	10	....	...	....	3.76	1.30	2.46	...	.....	.....	+++±	4.7	
3/ 9/29	15.9	0	Negative	.....	..	..	...	.....	....	....	4.6	22.7	....	....	....	193	3,810	1,500	+++	...	Ascites; "rest period"
3/10/29	15.0	0	Negative	110/ 68	68	..	...	.....	....	....	...	....	....	....	....	...	.....	.....	±	3.5	
3/11/29	15.0	0	Negative	.....	..	..	...	.....	....	....	...	....	....	....	....	...	.....	.....	0	...	
3/16/29	12.7	...	.....	.....	..	..	130	10.3	9	....	3.4	26	5.83	2.80	3.03	250	2,400	1,330	.....	...	
4/ 6/29	....	...	.....	.....	..	..	...	.....	....	....	...	....	....	....	....	...	.....	.....	.....	...	Animal killed (10 cc. ether intracardiac)

COMMENT

In this group of dogs, the removal of from 400 to 900 cc. of blood with the re-infusion of the cells from four to six times per week resulted, as the tables show, in gradual decrease in their serum protein. This reduction of the total protein occurred chiefly at the expense of the albumin fraction with a fairly rapid development of a reversion of the albumin-globulin ratio (fig. 1). After from four to six weeks of this continued loss of serum protein, the total blood protein was near 4.3 Gm., and the globulin fraction had increased to 3 or 3.3 Gm., while the albumin fraction had fallen to about 1 Gm. per hundred cubic centi-

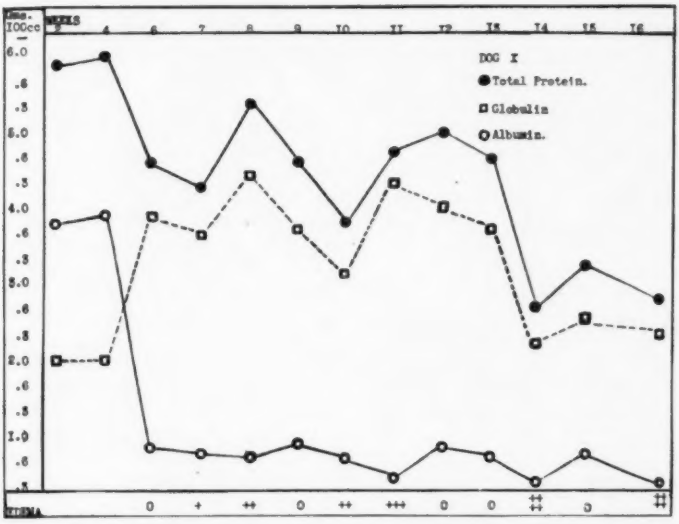

Fig. 1 (dog 1).—Chart illustrating the gradual changes of the total serum protein, the albumin and globulin fractions during plasmapheresis. By the sixth week the albumin-globulin ratio became inverted. By the seventh week there was a profound drop of the albumin fraction from 3.8 to 0.8 Gm. per hundred cubic centimeters. At the same time the serum globulin increased from a normal of 2 Gm. to 3.6 Gm. Throughout the remainder of the experiment the albumin was low and edema appeared whenever the albumin fraction fell below 0.7 Gm. per hundred cubic centimeters, independent of the total protein and globulin levels.

meters. After the animals had reached this depleted state, slight generalized subcutaneous pitting edema appeared. With the omission of plasmapheresis for even one or two days, this promptly disappeared. With the resumption of the process, the picture could be changed in from twenty-four to forty-eight hours from that of an edema-free animal to one with marked generalized anasarca. Since the shift of the edema

depended on the volume and frequency of the plasmapheresis, the dogs were carried repeatedly from the edema-free into the edematous state, and parallel determinations on the total protein, serum albumin and globulin fractions were made. These showed that, in spite of the large removal of the total proteins, the globulin fraction showed a definite increase, while the albumin fraction fell in direct proportion to the volume and frequency of the plasmapheresis. The most constant and striking observation, however, was that whenever the albumin fraction fell below 0.8 Gm. per hundred cubic centimeters, edema appeared. The lowest serum albumin observation was 0.41 Gm. per hundred cubic

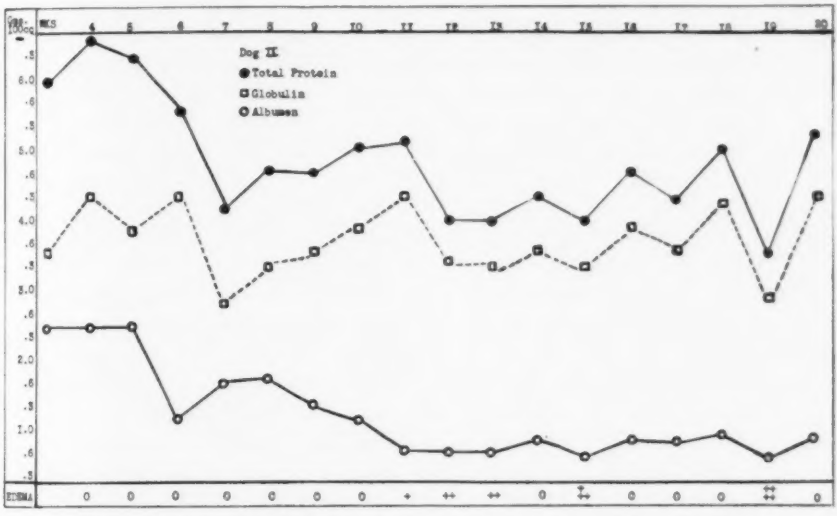

Fig. 2 (dog 2).—Chart illustrating the levels of total protein, globulin and albumin fractions in relation to edema during the course of plasmapheresis. Notice the constant association of the albumin level to edema occurring independently of the total protein and serum globulin.

centimeters. A reading of 0.6 Gm. per hundred cubic centimeters or less was always associated with ascites, pleural effusion, edema of the legs, prepuce and scrotum. All of this disappeared promptly when the albumin level rose above 1 Gm. per hundred cubic centimeters. This is well shown by the graphs on dogs 1 and 2 (figs. 1 and 2). These also indicate that edema occurred independent of the level of the globulin fraction and that the appearance of the edema was closely associated with the level of the albumin fraction. It was impossible to foretell the time of appearance and amount of edema by the total

protein level. It seemed, therefore, that, if only one blood determination was to be made, the albumin fraction was the informative one, and we soon came to look on it as the edema indicator. We spoke of this constant association of edema and the hypo-albuminemia of 0.8 Gm. as the "edema level."

A marked individual ability to stand plasmapheresis is indicated by the results obtained in this group of animals. Dog 2 was bled repeatedly, 900 cc. being drawn twice daily without the appearance of symptoms of hemorrhage or shock, while dog 3, even though much larger, was unable to stand an arteriosection of from 675 to 800 cc. without severe symptoms of hemorrhage. Similarly dog 4 showed evidence of collapse when from 400 to 675 cc. of blood was withdrawn, and he developed edema in five days following plasmapheresis. Evidence of damage to the kidney as indicated by a pathologic urinary sediment and albuminuria likewise appeared early in the latter two dogs. Our observations show that a complete recovery of the serum protein picture takes a matter of time somewhat in proportion to the severity and duration of the low proteinemia. At the beginning of the process, a return to normal took place within a few hours, but if the animal were carried to a more depleted state, a slower recovery followed. This was illustrated by dog 3. He was kept edematous for a period of one month and then allowed to recover. From the laboratory point of view and from the appearance of the dog, a complete recovery had taken place in four weeks (fig. 3).

In patients, we believe that albuminuria plays an extremely important rôle in the chronic edema of renal origin. We feel that the excessive loss of albumin in the urine in certain cases of nephritis in man stands in relation to low proteinemia and edema in man in a manner comparable to plasmapheresis and the formation of edema in our animals. In the one, the loss of serum protein is through the kidney, while in the other a loss occurred through active extraction from a peripheral vessel. However, the effect was similar with a comparable result so far as any experimental result may be applied to man.

A review of the cases of chronic nephritis with edema which have been admitted to the hospital and clinic during the past fifteen years shows that the albumin in the urine was frequently large in amount. In all of the cases that we have personally studied (twenty-seven) the loss of albumin in the urine has ranged from 5 to 60 Gm. per day. The greater the albuminuria, the more massive and more obstinate has been the edema. There is much evidence that the albumin, whether it is normal or abnormal, must come through the kidneys from the blood stream. Furthermore, if the loss is large enough, there follows a low-

ering of the total serum protein, particularly of the albumin fraction.[20] In our patients the loss of over 4 Gm. of albumin per day has been associated with a gradual drop of the total blood protein and when the serum albumin fraction in the blood fell to about 1 Gm. per hundred cubic centimeters, edema appeared. In the cases that we have been able to follow through such changes, this process required from six to eighteen months. Patient H^1 and Sp^1 (fig. 4) were particularly instructive in this respect. Both had a mild acute nephritis which soon subsided except for a well marked albuminuria and a relatively unimportant urinary sediment. The daily average loss of albumin was 8 and 15 Gm., respectively, and blood studies in them showed a gradual decrease in the

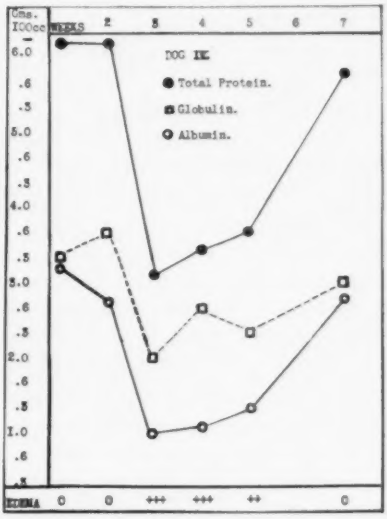

Fig. 3 (dog 4).—Chart illustrating the levels of total protein, albumin and globulin fractions in relation to edema during plasmapheresis. The first two weeks represents the period of control blood studies. On the fifth day of plasmapheresis edema occurred. The third week illustrates the low total protein and a marked fall of the albumin fraction with the occurrence of 3+ edema. Plasmapheresis was discontinued during the fourth week. The results for the fifth, sixth and seventh weeks illustrate a gradual return to normal of the total serum protein, albumin and globulin fractions.

20. Bright, Richard, quoted from Linder, Lundsgaard and Van Slyke, J. Exper. Med. **39**:887, 1924, Guys Hosp. Rep. **1**:848, 1836. Kisch, Franz: Eiweisskonzentration und Chlornatrium-Absorbtionsvermögen des blutserums Odematoser, Klin. Wchnschr. **1**:848, 1922. Linder, G. C.; Lundsgaard, C., and Van Slyke, D. D.: The Concentration of the Plasma Proteins in Nephritis, J. Exper. Med. **39**:887, 1924. Kollert, V., and Starlinger, W.: Ueber das Verteilungserhaltnis der Eiweiszkorpergruppen des Blutplasmas und Harnes bei Nierenkranken, Klin. Med. **104**:44, 1926.

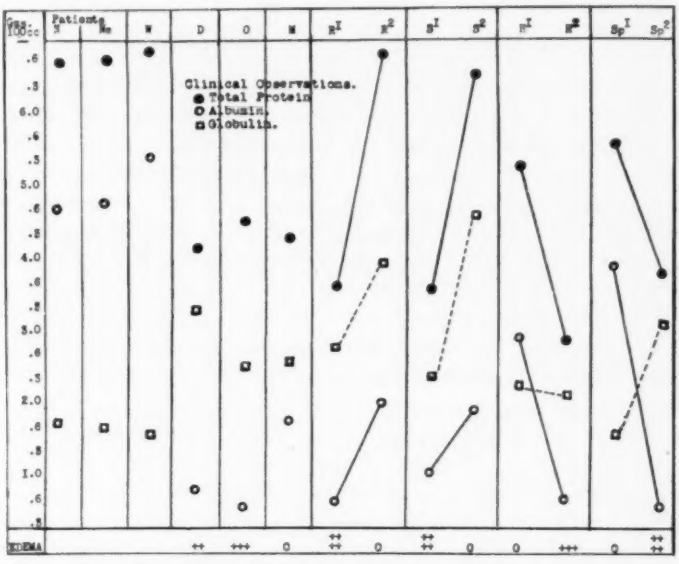

Fig. 4.—A series of cases, illustrating the levels of total serum protein, albumin and globulin fractions. *N* indicates a normal with total protein 7, albumin 5 and globulin 2 Gm. per hundred cubic centimeters; *Ne*, a case of chronic glomerular nephritis without edema showing normal levels of total protein, albumin and globulin; *W*, a case of chronic vascular nephritis with hypertension, showing normal levels of total protein, albumin and globulin; *D* and *O*, cases of chronic nephritis with edema, illustrating the typical blood observations in nephrosis. The total serum protein has dropped to 4 and 4.5 Gm. There is an increase of the globulin fraction and a profound drop of the albumin fraction with inversion of the ratio. The albumin fraction illustrates the relationship of a low albumin level to edema. *M* indicates results in a case of chronic nephritis without edema, illustrating a total protein as low as seen in the previous two cases but in which there is no edema. The albumin-globulin ratio is reversed, but the albumin fraction is not decreased to what is termed the edematous level. R^1 indicates results in a case of chronic nephritis with edema, illustrating the inversed albumin-globulin ratio, as low a total protein as in *M*, but in which the albumin fraction is much lower. This illustrates the relationship of a low albumin fraction to edema. R^2 is for the same case illustrating the return of total protein to a high normal level on a high protein feeding. The albumin-globulin ratio is still reversed, but the albumin fraction has become elevated so that the patient is edema-free. S^1 indicates a typical case of nephrosis. There is no antecedent history of acute nephritis. The total protein is markedly below normal, the albumin-globulin ratio is reversed. The albumin fraction is markedly decreased, and there is a generalized anasarca. S^2 is for the same case illustrating the results of a high protein diet. H^1 and Sp^1 show the results in cases of acute nephritis. H^2 and Sp^2 are for the same cases after from six to eighteen months of a marked albuminuria in which the patients developed changes typical of nephrosis. There is a profound drop in the total protein, the albumin-globulin ratio is reversed, but the albumin fraction dropped below 1 Gm. per hundred cubic centimeters with the formation of edema. (It is interesting to note that if lines were drawn to connect the total protein, albumin and globulin fractions of these cases that a chart would result that is similar to figures 1 and 2 of dogs 1 and 4, respectively.)

total protein with an inversion of the albumin to globulin ration (H^2 and Sp^2, fig. 4). Finally after eighteen and six months, respectively, their serum albumin fractions had fallen well below 1 Gm. per hundred cubic centimeters with the appearance of marked generalized anasarca together with all of the observations regarded as characteristic of nephrosis.

It was of interest to be able to estimate the presence of and the amount of the edema in any renal patient by the determination of the serum albumin in a given specimen. Edema appeared at about 1 Gm. per hundred cubic centimeters of blood and increased rapidly as the albumin fraction decreased so that 0.5 Gm. per hundred cubic centimeters of blood was always associated with marked generalized anasarca, ascites and pleural effusion. Conversely, edema decreased shortly after the albumin fraction increased above 1 Gm. level. Cases B^1 and S^1 (fig. 4), illustrate this point and show the occasional improvement following dietary therapy. These patients were admitted to the hospital showing pallor, weakness, muscular wasting, marked anasarca, ascites, pleural effusion and albuminuria similar to cases D and O (fig. 4). The blood serum pictures were characteristic, and the patients were in negative nitrogen balance, as many of these cases were found to be, particularly if they have been restricted in their protein intake. On a liberal diet, high in protein, nitrogen began to be stored in quantities varying from 8 to 24 Gm. per day, and they soon passed into nitrogen equilibrium. At the same time there was a gradual increase in the serum albumin and serum globulin (B^2 and S^2, fig. 4). Edema disappeared rather quickly, and the patients rapidly gained weight and strength and were able to go about their usual work. A comparative study of figures 1, 2 and 4 will show these clinical and experimental observations to be remarkably parallel.

The formation of the serum protein is of great interest and indicates the danger of the constant loss of albumin in even relatively small amounts. The daily average loss of globulin in dogs 3 and 2 was 10.8 Gm., while the average loss of albumin was 4.3 Gm. per day (computed by determining the albumin and globulin content of the serum discarded at each time of plasmapheresis). The globulin showed a great increase during the continued plasmapheresis, while the albumin remained at a low level. This probably indicates a rapid regenerative power on the part of the body to form serum globulin, while the serum albumin is replaced much less readily. It is not surprising, therefore, that any patient who is losing over 15 Gm. of albumin in the urine per day loses ground rapidly. At first glance the repeated extraction of so much serum from our dogs may appear to be extreme and not at all comparable to what occurs in man. A slight calculation, however, will

show that what we did to our dogs is mild in comparison to what happens in the patients with nephrosis. The dogs lost only 15.1 Gm. of albumin and globulin on the days of plasmapheresis, whereas the patients lost from 15 to 20 Gm. per day of albumin (albumin and globulin) in the urine. The amount of urinary globulin is usually small.[21] A patient losing from 15 to 20 Gm. of albumin (albumin and globulin) per day is suffering a relative loss which is from two to three times greater than in our dogs.

The marked variation in the amount of albumin (albumin and globulin) lost by each patient (5 to 60 Gm. per day), together with the apparent individual ability both to withstand and to replace the loss of protein, explains in part the frequent failure of a high protein diet to supply the deficiency. Roughly, those patients losing under 10 Gm. of albumin and globulin per day have shown remarkable benefit from the taking of a liberal diet high in protein. Just what effect this improvement will have on the pathologic process only time will tell. However, those patients losing over 20 Gm. in the urine have rapidly progressed into renal insufficiency in spite of anything we have been able to do.

There has been considerable controversy concerning the basal metabolism in relation to nephrosis. Most authors have reported a low metabolism in patients, and many have seen good results from the administration of thyroid, such as elevation of metabolism and loss of edema. Metabolic studies were made on the dogs as described in the foregoing. In general there was a marked fall in the metabolic rate after the second or third week of plasmapheresis. The lowered metabolism occurred as the total serum protein began to fall; and this happened before the appearance of edema or changes in the urine. When the dogs were in a condition of generalized anasarca with pleural effusion, the metabolism estimates were unsatisfactory due to the dyspnea and restlessness.

The basal metabolic studies on dog 1 showed a gradual fall from 190 to 140 calories per kilogram hour. This represented the second stage of study up to the time of nephrectomy. After nephrectomy the basal metabolic rate returned to 155 calories from which level the rate gradually fell to 115 when plasmapheresis was resumed (fig. 5).

Dog 2 after the second week of metabolic studies showed a gradual fall from 160 calories to a low level of 120 (fig. 5).

The metabolic studies made on dog 4 during the first two weeks revealed a normal basal metabolic rate of 250 calories per kilogram hour. One week after plasmapheresis, the metabolic rate had dropped to a level of 230 calories. At the end of the period of plasmapheresis, the

21. Hiller, Alma; McIntosh, J. F., and Van Slyke, D. D.: The Excretion of Albumin and Globulin in Nephritis, J. Clin. Investigation **4**:235 (June) 1927.

metabolic rate showed a definite further fall to 193 calories. From this time until the autopsy was performed, the removal of blood was omitted, and the dog was allowed to rest. The basal metabolism at the end of this rest period had returned to the normal rate of 250 (fig. 5).

The majority of our patients had a decreased basal metabolic rate varying from 0 to — 35, and was lowest when edema was the greatest. The mere presence of edema, increased weight and body surface seemed not to be entirely responsible for the fall in the metabolic rate. Zero readings were observed in an occasional patient with moderate generalized anasarca. Conversely, metabolic determinations of from — 25 to — 35 during the acute stage of edema were observed which shifted

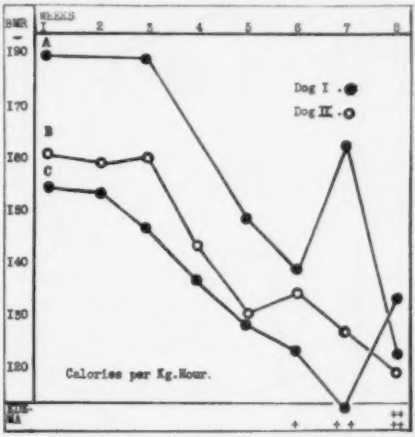

Fig. 5.—Illustration of basal metabolic studies. *A* represents the basal metabolism of dog 1 during the first period of plasmapheresis up to nephrectomy. Following this there was a postoperative rise to 165 which subsequently dropped to 120 calories per kilogram hour. *C* represents the return of the basal metabolism to 155 calories during the four weeks of convalescence. Plasmapheresis was resumed and there was a second gradual decrease of the metabolic rate to 108. *B* is the curve for dog 2 illustrating the gradual decrease of the basal metabolism from 160 to 120 calories per kilogram hour. The gradual and marked fall of the basal metabolism of the dogs during plasmapheresis was parallel with the gradual serum depletion, and occurred before the appearance of edema and urinary changes.

only slightly (from — 20 to — 25) after the patient became edema-free. Regardless of this lowered metabolism, most of our patients showed no improvement under thyroid therapy with doses varying from 1 to 50 grains per day. Occasionally, there was a mild diuresis with a transient loss of some of the edema.

The observations made of metabolism, in the patients and dogs, suggest that the lowered basal metabolic rate may be only a protective measure. An abnormal body metabolism may have resulted and may be a primary factor in the production of the experimental and clinical pathologic observations. In view of a lack of pathologic changes in the thyroids of our dogs, we are not justified at this time in saying more than that the lowered basal metabolic rate is probably only a protective mechanism as seen in inanition and starvation.

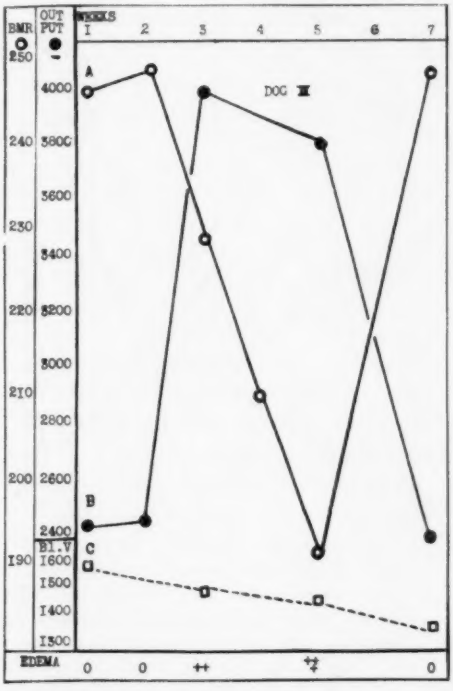

Fig. 6 (dog 4).—*A* indicates the basal metabolic rate; *B*, the cardiac output, and *C*, the blood volume. The profound drop of the metabolic rate, the marked increase of the cardiac output and the relative constancy of the blood volume during the period of plasmapheresis as shown in figure 3 are illustrated. There is a return of the metabolic rate and cardiac output to the normal during the rest period.

There is a general opinion that the blood volume does not change in cases of nephrosis and that if changes do occur, it is only in the severely anemic patients.[22] Others have referred to nephrosis as a hyemic type

22. Brown, G. E., and Rowntree, L. G.: Blood Volume in Glomerular Nephritis and Nephrosi, Arch. Int. Med. **14**:44 (Jan.) 1928.

of nephritis, suggesting an increase of the blood volume [23] (*27*). Figures 6 and 7 illustrate the blood volume in our dogs during plasmapheresis. These experimental studies confirm the general opinion that no changes occur in the blood volume in nephrosis. Dogs 1 and 2 (fig. 7) showed no definite changes from the normal blood volume of 1,500 cc. and 1,900 cc., respectively. Dogs 4 and 5 showed essentially the same results, i. e., plasmapheresis, edema, etc., had no effect on the blood volume.

Studies of cardiac output were made in conjunction with the studies of basal metabolism and blood volume. The cardiac output depends on

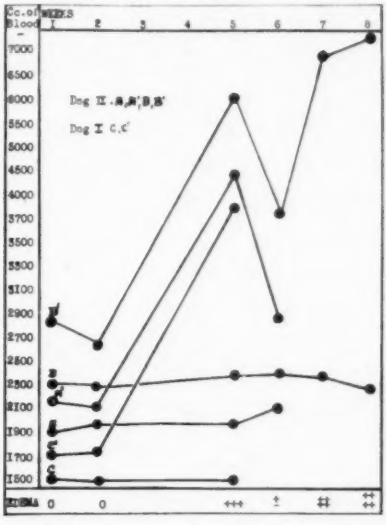

Fig. 7.—Composite chart of dogs 1 and 2 illustrating the increase of the cardiac output and the constant level of blood volume during plasmapheresis. *A* and A^1 represent the blood volume and the cardiac output of dog 2 during five weeks of bleeding followed by four weeks of rest. *B* and B^1 show the changes during a second period of plasmapheresis on dog 2. At the period of greatest edema the cardiac output increased to 7,000 and 7,800 cc. per minute. The two lines at the bottom of the chart represent the blood volume (*c*) and cardiac output (c^1) on dog 1 during five weeks of study. These observations indicate that the cardiac output is greatly increased during periods of edema of this kind, while the blood volume is not grossly affected.

the difference of oxygen content of arterial and venous blood which was obtained from the heart. There was a definite marked increase of

23. Wright, Samson: Applied Physiology, ed. 2, Humphery Mulford, London, Oxford University Press, 1928, p. 307.

cardiac output in proportion to the amount of edema. (Figure 6 is a composite chart on dog 4, illustrating the cardiac output in comparison to changes of metabolism and blood volume. It shows the marked increase of cardiac output during the stage of edema and return to normal during the edema-free period.) Figure 7 illustrates the uniformity of change in cardiac output in different dogs under similar conditions as

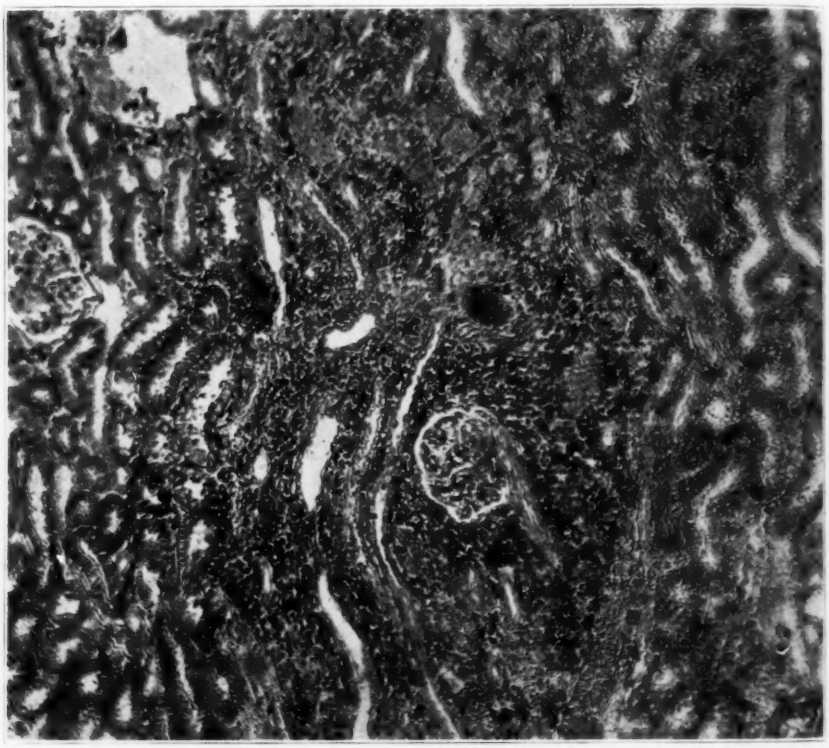

Fig. 8 (dog 1, nephrectomized kidney).—This kidney section as well as all the others was stained with eosin and methylene blue, except the last section (fig. 13), which was stained with scharlach R and slightly counterstained with hematoxylin. The microscopic study of the kidney of dog 1 illustrates moderate degree of swelling and desquamation of the tubular epithelium, definite areas of plasma cell infiltration and a rare glomerulus that shows hyalinization of Bowen's capsule. The tubules in areas of plasma cell infiltration are markedly damaged. Magnification, × 1565.

produced by plasmapheresis. In dog 1 (fig. 7) the normal cardiac output was 1,700 cc. per minute. At the time of marked edema, the cardiac output rose to 3,800 cc. per minute. In dog 2, the normal cardiac out-

put was 2,200 cc. which rose to 4,500 cc. and dropped as the edema decreased to 2,900 cc. As the edema reformed, the cardiac output rose to 6,000 cc. of blood per minute (fig. 7). As massive edema was produced, the cardiac output increased markedly to 7,000 and to 7,800 cc. per minute.

The physiologic significance of such increased cardiac output in relation to edema is rather difficult to explain. It may be the result of a

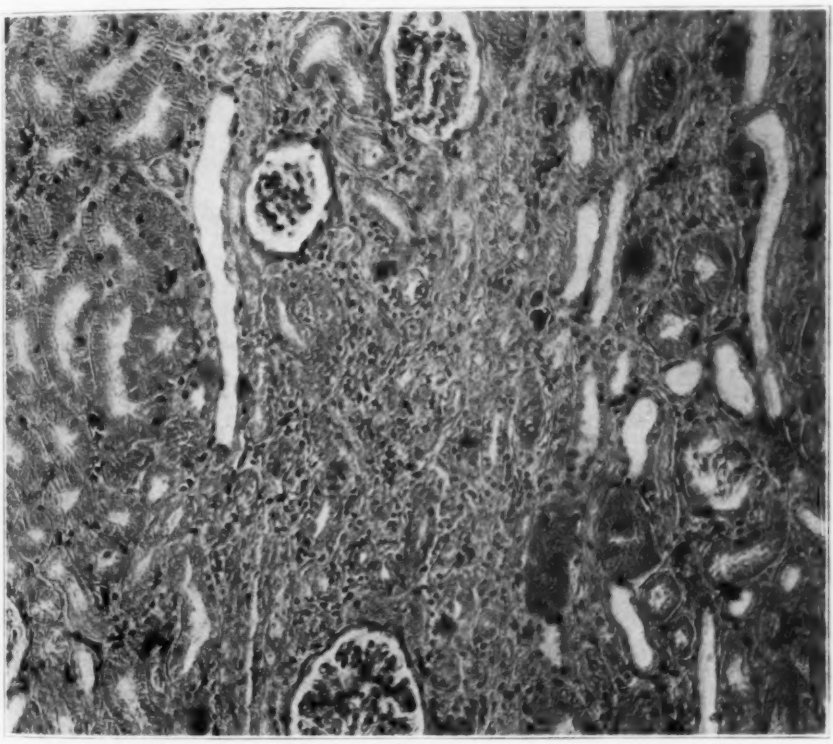

Fig. 9 (dog 1, autopsied kidney).—This section demonstrates marked progression of renal pathologic changes. Disintegration and atrophy of tubular epithelium are markedly increased. There are numerous areas of lymphoid and plasma cell infiltration and definite connective tissue replacement. Many glomeruli show thickening and hyalinization of the capsule with more glomerular atrophy than was seen previously. Magnification, × 1758.

general change that is occurring in the body tissues in which there is a definite oxygen want. It may be due to the tissue demands for more nourishment, as there is a markedly low proteinemia during the greatest changes in the cardiac output. However, the oxygen carrying capacity

of the red blood cells may have been altered so that the increase of cardiac output obtained may not be an actual one.

The cholesterol, phosphorus and calcium changes in the blood are considered typical of nephrosis. Their determinations are of diagnostic interest and therefore were studied in our dogs during plasmapheresis. The cholesterol increased to as high as 254 mg. per hundred cubic centimeters. In patients with nephrosis observations of cholesterol

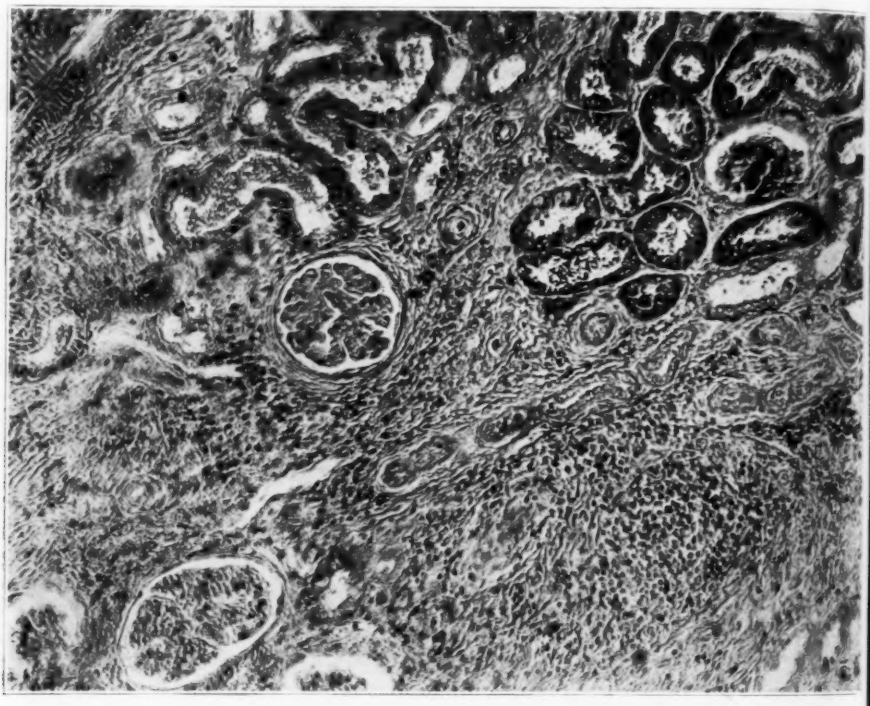

Fig. 10 (dog 2).—This kidney section shows that the predominating lesion is in the tubular region. The tubular epithelium shows marked cloudy swelling and desquamation. Definite areas of plasma and lymphoid cells accompanying areas of scar tissue replacement throughout the tubular region are demonstrated. Rather frequently atrophied glomeruli with marked thickening of the capsule can be seen. Magnification, × 1635.

determinations always showed an increase. This varied from 300 to 800 mg. Phosphorus in our dogs increased from a normal of 4 and 4.5 mg. to as high as 24 mg. This was comparable to the determinations made in our patients. The calcium determinations in the dogs showed a decrease from 10.25 to 9.25 mg. per hundred cubic centimeters. In

patients with nephrosis the calcium was frequently observed as low as 8.25 mg. Efforts to maintain normal calcium metabolism in our patients by the administration of calcium or parathyroid extract were of no avail. Fibrinogen determinations were made on the dogs and showed an increase in the edematous stages to as high as 1.2 Gm. per hundred cubic centimeters of blood serum. The patients with marked edema showed a similar increase in fibrinogen from 10 to 300 per cent.

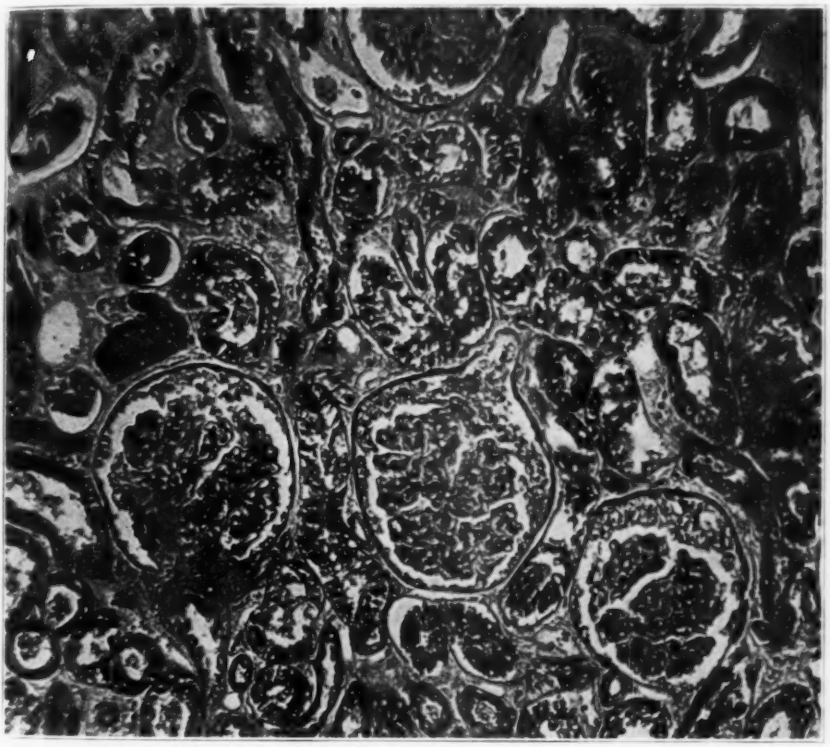

Fig. 11 (dog 3).—This kidney represents the earliest stage in the progressive lesion demonstrated in this series of animals. The tubules show cloudy swelling with slight desquamation of the epithelium in the convoluted portion. In many of the luminae can be seen hyaline and fatty casts. The glomeruli were normal except for a slight thickening of the capsule. A precipitate was seen in the capsular spaces (possible albumin) streaming down into the tubules. Magnification, × 2133.

Urinalysis of the dogs after plasmapheresis was begun and after the appearance of edema, showed albumin, hyaline and granular casts, fat droplets, rare red and white blood cells and renal epithelial cells. The

specific gravities averaged between 1.030 and 1.040. In dogs 1, 2 and 3, as they became more and more depleted and as greater amounts of edema occurred, the urinary observations increased. Especially was this true of the granular casts. Late in the experimental studies of dogs 1 and 2, the specific gravity of the urine fell to 1.010 and the blood pressure rose from normals of 130 and 140 systolic and 80 diastolic to as high as 170 to 190 systolic and 90 to 110 diastolic. At this time, the

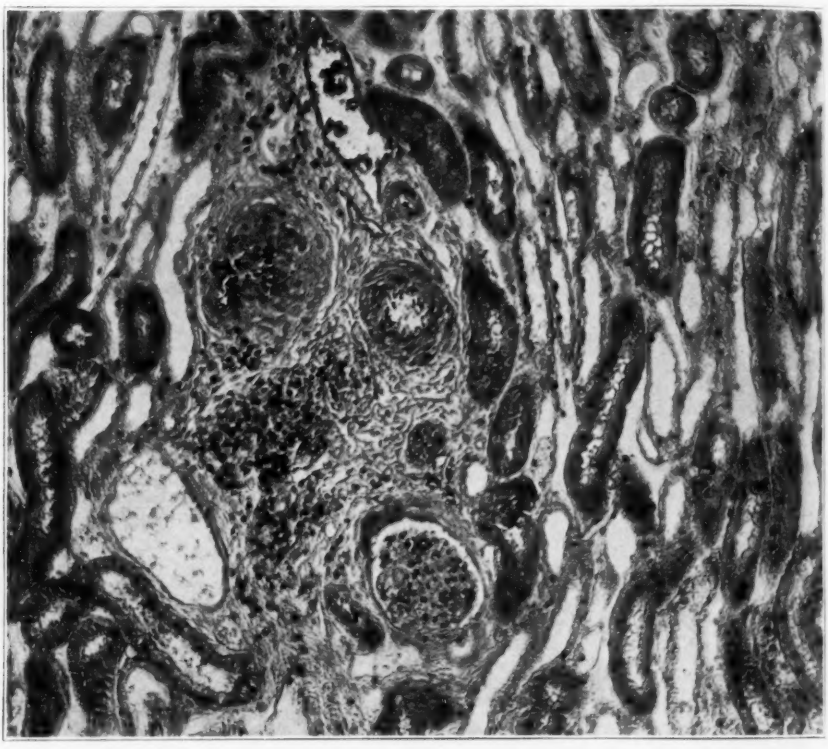

Fig. 12 (dog 4).—This kidney section demonstrates a predominating tubular lesion with a markedly swollen and desquamated epithelium. The tubules contain occasional hyaline and fatty casts. There are definite areas of small round cell infiltration accompanying a slight amount of scar tissue formation. Occasionally a glomerulus shows marked atrophy, hyalinization and thickening of the capsule. Mitotic figures were found in the tubular and glomerular epithelium. Magnification, × 1600.

former amount of edema could not be maintained in dog 3 and was maintained in dog 2 only by increasing the frequency of plasmapheresis and by increasing the amounts of blood withdrawn nine fold.

The urinary and blood pressure changes as described previously served as an index of a progressive kidney damage in our dogs. The experimental results tend to support the theory that the continual loss of albumin in the urine is sufficient alone to produce renal pathologic changes. The kidneys of the dogs showed pathologic changes varying from slight cloudy swelling of the tubules, fatty, small round cell and plasma cell infiltration to marked tubular destruction, scar tissue replacement and glomeruler atrophy. In the later stages the tubular atrophy, interstitial connective tissue deposits and glomerular changes were definite (figs. 8, 9, 10, 11, 12 and 13).

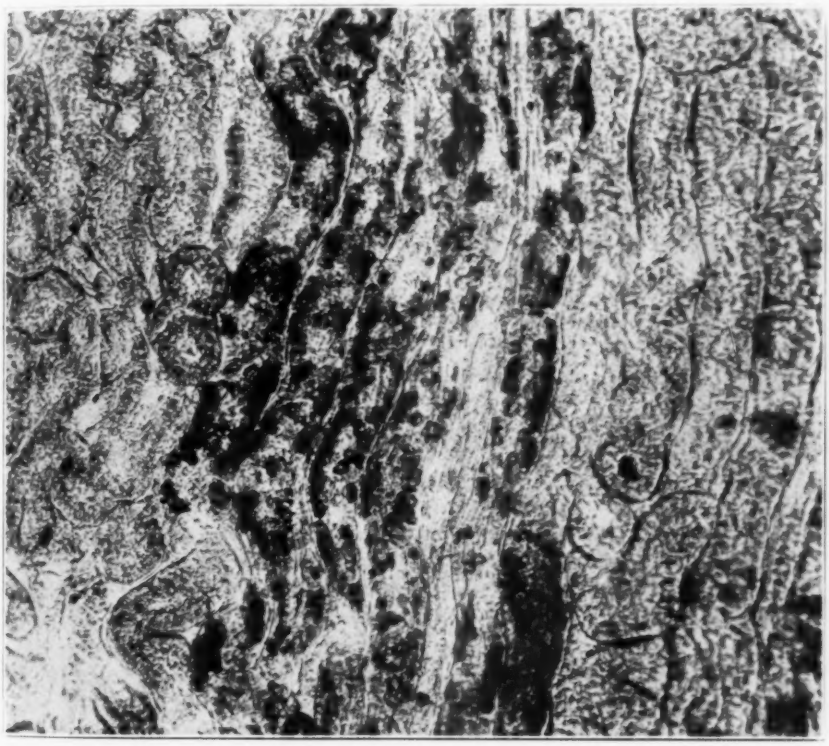

Fig. 13 (dog 4).—This kidney section (stained with scharlack R) demonstrates definitely the marked fatty infiltration or degeneration that occurred in these animals. The dark appearing stains in the tubules represent the fat. Magnification, × 2000.

In our patients we feel that the early kidney change is predominantly a tubular one, and that the primary lesion was due to acute nephritis or

as in a few cases was obscured. After a variable period of time of albuminuria, the serum depletion occurred, and edema and the rest of the picture typical of nephrosis appeared. These patients usually do not die at this stage unless some severe intercurrent infection to which they are predisposed, develops. After a variable length of time of such an albuminuria, edema, etc., the blood pressure increases, the heart enlarges, changes in the eyegrounds occur, the results of renal function tests decrease, the blood urea nitrogen increases, the amount of albumin in the urine diminishes, casts and cellular elements increase, edema disappears and the disease picture gradually passes from one of tubular nephritis to one of glomerular changes; finally, the patient dies of uremia. The pathologic change in the kidney is one of a chronic mixed or diffused nephritis with marked tubular, glomerular and interstitial changes.

CONCLUSIONS

1. Edema in dogs, varying from a slight to a marked degree, can be produced by decreasing their serum protein.

2. The amount of edema both in patients and in dogs seems more closely associated with the level of the serum albumin fraction than with the total protein.

3. The basal metabolism of the dogs fell with the depletion of the blood serum.

4. The blood volume in dogs was unchanged in the edematous period, but the cardiac output was greatly increased.

5. Renal pathologic changes in dogs were produced by a low proteinemia, as shown by the appearance in the urine of albumin, granular casts, fat droplets and products of renal cell degeneration in the urine and by definite degeneration of the renal tubules, destruction of the glomeruli and scar tissue formation.

THE SEROLOGIC AND ETIOLOGIC SPECIFICITY OF THE ALPHA STREPTOCOCCUS OF GASTRIC ULCER

A BACTERIOLOGIC STUDY *

EDWARD WATTS SAUNDERS, M.D.
WITH THE TECHNICAL ASSISTANCE OF MARY A. COOPER, B.S.
NEW YORK

Because of the overwhelming trend of clinical opinion that infection is the inciting cause of gastric, duodenal and gastrojejunal ulcer, the present investigative work was undertaken by the Department of Surgical Research of Cornell University Medical College, New York City, in collaboration with the Department of Public Health and Preventive Medicine under the direct supervision of Dr. Joshua E. Sweet, Dr. John C. Torrey and Dr. Morton C. Kahn.

The work involved a bacteriologic study of gastric ulcer and the isolation of an alpha streptococcus from gastric, duodenal and gastrojejunal ulcers which is proved identical and specific by differential cultural tests and by agglutination, cross-agglutination and agglutinin absorption. The agglutinogenic and antigenic homogeneity of this type with four alpha strains, which were obtained from cases of a specific disease characterized by an acute onset of multiple typical ulcers of the lip, tongue, soft palate and pharynx, is demonstrated, and also its morphologic likeness to, but cultural and serologic difference from, all alpha strains obtained from other foci in the mouth. A comparison is also made with alpha-prime strains isolated from ulcers resulting from contact with human mouths. It is further shown that serums from patients with proved gastric, duodenal or gastrojejunal ulcer contain specific agglutinins for this alpha streptococcus type, whereas serums from patients with other streptococcal diseases fail to agglutinate it or only in low titer. Observations are also recorded as regards its pathogenic characteristics, as shown by animal inoculations. On the basis of this evidence, the theory that gastric ulcer is a specific infection is offered.

LITERATURE

Etiologic Factors Other Than Infection.—Ulcer of the stomach has been produced experimentally by many different methods, some so foreign to possible etiology in man that they will only be cited. Other

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methods employed have had a definite bearing on location and chronicity but probably not on etiology. Mann [1] stated that, "Chronic peptic ulcers appear to have never been consistently produced experimentally in the gastric mucosa by any method." Complete bibliographies have been compiled repeatedly, and reference may be made to those of Bolton,[2] Greggio,[3] Ivy,[4] Butsch,[5] Durante,[6] Rosenow,[7] and recently Morton [8] and Nickel.[9] Nickel mentioned the following extraneous methods of production: interference with the nerve supply, section of the spinal cord, section or stimulation of the vagus or sympathetic nerves, injury of the mucosa mechanically, by excising pieces, by the use of sutures, by application of the actual cautery, silver nitrate and nitric acid, by the injection into or beneath the mucosa of such substances as foreign protein in sensitized animals, gastro-toxic serum, silver nitrate and alcohol, injection of lead chromate and fat to produce embolic lesions, by intravenous injections of poisons, such as pilocarpine, phenol, chloroform, bile salts, epinephrine, diphtheria toxin, filtrates of various bacteria and by extirpation of the suprarenal and thyroid glands, a disproportion between the gastric pepsin and the antipepsin of the blood serum, roentgen rays, spasms or portal stasis giving rise to hemorrhagic infarction and subsequent ulceration.

In 1853, Virchow initiated the idea that functional disturbances, such as hypotonia and hypertonia, have produced lessened resistance by

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1. Mann, F. C., and Williamson, C. S.: The Experimental Production of Gastric Ulcer, Ann. Surg. **77**:409, 1923.

2. Bolton, C.: Experimental Production of Gastric Ulceration by Injection of Gastric Toxin, Lancet **1**:1330, 1908.

3. Greggio, Etorre: Des ulcers gastro-duodenaux, Arch. de méd. expér. et d'anat. path. **27**:533, 1916-1917.

4. Ivy, A. C., and Shapiro, P. F.: Experimental Production of Gastric Ulcer by Local Allergy; Preliminary Report, J. A. M. A. **85**:1131 (Oct. 10) 1925.

5. Butsch, J. L.: Ulcers of the Gastro-Intestinal Tract with Special Reference to Gastro-Jejunal Ulcers, Papers from the Mayo Foundation and Medical School of the University of Minnesota **1**:57, 1915-1920.

6. Durante, L.: The Trophic Element in the Origin of Gastric Ulcer, Surg. Gynec. Obst. **22**:399, 1916.

7. Rosenow, E. C.: The Production of Ulcer of the Stomach by the Injection of Streptococci, J. A. M. A. **61**:1947 (Nov. 29) 1913; The Causation of Gastric and Duodenal Ulcer by Streptococci, J. Infect. Dis. **19**:333, 1916; Specificity of Streptococcus of Gastroduodenal Ulcer and Certain Factors Determining Its Localization, ibid. **33**:248, 1923; Transmutations within the Streptococcus Pneumococcus Group, ibid. **1**:14, 1914.

8. Morton, C. B.: Observations on Peptic Ulcer; A Method of Producing Chronic Gastric Ulcer; A Consideration of Etiology, Ann. Surg. **85**:207, 1927; Healing of Experimental Peptic Ulcer After Gastro-Enterostomy, Ann. Surg. **85**: 230, 1927.

9. Nickel, A. C., and Hufford, A. R.: Elective Localization of Streptococci Isolated from Cases of Peptic Ulcer, Arch. Int. Med. **41**:210 (Feb.) 1928.

interfering with the nerve or blood supply and have resulted in ulceration by digestion. Hamburger [10] stated that abrasions resulting from traumatization by food or from emboli produce acute ulceration which in the presence of hypersecretion and hyperacidity from some underlying cause, such as vagotonia or reflex pylorospasm, may produce chronic ulcers. Wilkie [11] stated that toxic absorption from the appendix or colon could produce an irritable condition of the autonomic nervous system with a tendency to ulcer formation. Intravenous injection of toxins isolated from animals with high intestinal obstruction and the possibility of aberrant islands of intestinal glands in the stomach and duodenum which would be digested by the acid of the stomach were suggested by Sweet [12] and his co-workers as a possible pathogenesis. The most consistent experimental observations have been those of Mann and Williamson [1] and Charles Morton.[8] These investigators have been able to produce subacute or chronic peptic ulcer quite comparable to that found in man by devising a method to divert those secretions which neutralize the gastric juice as it leaves the stomach to another portion of the intestine removed from the point of emergence of the acid. The ulcers developed in the intestinal mucosa just adjacent to the gastric mucosa in a high percentage of cases. This type of ulcer produced by surgical duodenal drainage could then be healed by gastrojejunostomy and pyloric exclusion, which completely protected the ulcers from any exposure to acid chyme. All acute lesions produced experimentally without surgical duodenal drainage heal rapidly. Morton [8] excised pieces of mucosa in different sites of the stomach and then instituted surgical duodenal drainage. The most chronic ulcers formed on the lesser curvature and pylorus. Healing of the ulcers ensued when measures were taken to reintroduce alkali in the region of the ulcer or when the forces of the acid ejections of the stomach were diffused or counteracted.

Durante [6] stated that ulcer could be produced by any agent capable of damaging the sympathetic nervous system which controlled circulation, secretion and profound sensibility in the stomach on which the very life of the gastric cell may be said to depend. The theory of trophic ulcer must be taken in this sense.

Friedman [13] stated that in the dog chronic ulcers may arise from acute ulceration if certain factors are present, namely, prolonged and

10. Hamburger, W. W.: Discussion on Experimental Studies in the Production of Chronic Gastric Ulcer, M. Rec. **86**:898, 1914.

11. Wilkie, D. P. D.: Observations on the Etiology and Pathology of Duodenal Ulcer, Edinburgh M. J. **13**:196, 1914.

12. Sweet, J. E., and others: The Pathogenesis of Peptic Ulcer, Arch. Surg. **6**: 837 (May) 1923.

13. Friedman, J. C.: Experimental Chronic Gastric Ulcer, J. A. M. A. **63**:380 (Aug. 1) 1914.

probably violent action of active gastric juice (hypersecretion and hyperperistalsis), and that some ulcers may remain unhealed if the acidity later drops to normal. Other factors, such as anemia, absence of antipepsin and vascular obstruction, are unnecessary suppositions. He believed that Stromyer's theory of the digestive action of the gastric juice and the progress of food particles is probably correct.

Dragstedt and Vaughn [14] produced chronic ulcers by the injection of silver nitrate and laying in sutures in the mucosa. The lesions caused a hypersecretion of gastric juice and healed more rapidly under alkali therapy.

The Relation of Infection to the Formation of Gastric Ulcer.—Broussais in 1823 [15] and Abercrombie in 1824 [16] described gastric ulcers as inflammatory conditions and ulcerations of the stomach. J. Cruveilhier,[17] who is recognized by the French as the first to describe this disease fully, in 1830 gave complete gross morbid pathologic descriptions of ulcer of the stomach and described their inflammatory appearance. In 1838, Albers [18] described the pathology of ulcers. Ulcer was considered by Lebert [19] in 1857 and by Cohn [20] in 1860 to occur as a part of a general pyemia by the intravenous injections of pus. Gandy [21] stated that G. Colombo [22] in 1877 showed evidence of the existence of inflammation in many ulcers of the stomach. In 1874, Böttcher [23] first reported micro-organisms found in ulcer. M. Letulle [24] in 1888 produced gastric ulceration by injection of *Cultures microbiennes,* probably streptococci and staphylococci. He also found colonies of micro-organisms in stained sections of ulcers. M. Gilbert,[15] Claude,[15] Favre,[15] Hal-

14. Dragstedt, L. R., and Vaughn, A. M.: Gastric Ulcer Studies, Arch. Surg. **8**:791 (May) 1924.

15. Quoted by Gandy.

16. Abercrombie: Inflammatory Affections and Ulceration of the Stomach, Edinburgh M. & S. J. **21**:1 (Jan.) 1824.

17. Cruveilhier, J.: De l'ulcere simple chronique de l'estomac, Atlas d'anatomie pathologique du corps humain, 1830, no. 10; Traite d'anatomie pathologique générale, Paris, J. B. Bailliere et Fils, 1864.

18. Albers, J. H. F.: Beobachtungen auf dem Gebiete der Pathologie und pathologischen Anatomie, Bonn, 1838.

19. Lebert: Traité d'anat. path. **1**:537, 1857.

20. Cohn: Klinik der embolischen Gefässkrankheiten, 1860, p. 523; quoted by Rosenow.

21. Gandy, Charles: L'ulcères gastrique, Thesis de la Faculté de Médicine, Paris, 1899, vol. 21; Paris, G. Steinheit, 1899, no. 592, p. 276.

22. Colombo, G.: Patogenesi dell ulcera cronica o perforante dello stomaco, Annali universali di medicina e chirurgia, 1877, p. 239.

23. Böttcher, H.: Zur Genese des perforierten Magengeschwürs, Dorpat. med. Ztschr. **5**:148, 1874.

24. Letulle, M.: Origine infectieuse de certains ulcères simples de l'estomac ou du duodenum, Bull. et mém. Soc. méd. d. hôp. de Paris **5**:360, 1888.

lion,[15] Wurtz [15] and Charrin [15] all obtained lesions in the stomach by the experimental injection of different organisms and toxins of organisms, *B. pyocyaneus*, diphtheria bacillus and *B. coli*. In 1894, Favre [15] produced ulcers in the stomachs of animals by the intravenous injection of a blood culture of a patient dying in eclampsia and with erosions and ulcerations of the stomach. Gaillard,[25] in 1882, described micro-organisms in the tissue of ulcers. Sydney Martin,[15] in 1895, stated that lesions of the stomach were identical "avec la necrose bacterienne." In 1898, Henkel [15] stated that a case of ulcer of the stomach was due to a streptococcus found in the border of this ulcer. From 1880 to 1890, Gaillard,[25] Letulle,[24] Widal,[15] Gandy [21] and Dieulafoy [15] endeavored, by citing observations and by experimental work, to show that simple ulcer was infectious in origin. These workers isolated a streptococcus three times, but with fresh cultures they were not able to produce the lesion in the rabbit. In 1899, Bezancon and Griffon [26] reported the production of ulcers in the rabbit's stomach by the injection of pneumococci. In 1901, Gordon [27] advocated infection as the cause of gastric ulcer and supported his claim with photomicrographs showing micrococci and chronic inflammation in ulcers. He believed the course to be bacterial necrosis, the necrosing area dropping out and being followed by further necrosis as a result of acid, leaving a punched-out ulcer. Dudgeon and Sargeant,[28] in 1905, isolated a diplostreptococcus from four out of nine cases of peritonitis following perforated gastric ulcer. The same organism was found in sections from the edge of the ulcer. They stated that it sometimes grew in chains. In 1906, Turck [29] claimed to have produced ulcers by feeding *B. coli communis* for a varying length of time to dogs. In 1913, Bolton [30] stated that probably the commonest cause of necrosis of the mucous membrane and resulting ulcer of the stomach is bacterial infection, that the infection occurs through the blood stream and that the necrosis is due to the direct effect on the tissues of the bacterial poison alone or together with the gastric juice

Rosenow's [7] first report appeared in 1913, when he claimed that streptococci quite irrespective of their original source, when of a certain grade of virulence, exhibited affinity for the gastric mucous membrane, producing a localized infection and ulcer. He believed that the organisms were carried by the blood stream, not ingested. In 1915, Rosenow and

25. Gaillard, S.: Essai sur la pathogenie de l'ulcére simple de l'estomac, Thèse, Arch. gén. de méd. **7**:205 (Aug.) 1882.

26. Bezancon and Griffon: Bull. et mém. Soc. anat. de Paris **1**:409, 1899.

27. Gordon, W.: The Origin of Gastric Ulcer, Bristol M.-Chir. J. **19**:100, 1901.

28. Dudgeon and Sargeant: The Bacteriology of Peritonitis, London, Archibald Constable, Lt., 1905, p. 58.

29. Turck, F. B.: Ulcer of the Stomach, J. A. M. A. **46**:1753 (June 9) 1906.

30. Bolton, Charles: Ulcer of the Stomach, London, Arnold, 1913, p. 396.

Sanford [7] made cultures from the wall of ulcers in twenty-four cases. Streptococci were isolated in pure culture from nine and in mixed culture from all of the rest, nonhemolyzing staphylococci from ten cases and *Bacillus welchii* and *B. coli* in some. Four adjacent lymph glands yielded streptococci in pure culture. These authors stated that the strain from twenty-seven cases, all of chronic ulcer, produced relatively short chains and diplococci and a diffuse turbidity with much acid in dextrose and ascites broth. All streptococci from relatively acute ulcers produced typical green colonies on blood plates and usually long chains in dextrose broth. Streptococci were never grown from the normal stomach wall. In 1916, Rosenow [7] reported that streptococci had been demonstrated in the tissue or isolated in pure culture from forty-two of fifty-four typical chronic ulcers in man. From a careful review of the article, it appears that the streptococcus was isolated six times and demonstrated in the tissue thirty-six times, as information in regard to culture was supplied in only six cases. The description of the organism states that it produced small, moist, nonadherent, discrete, grayish colonies on blood plates and short chains and masses of coccus-like forms, a diffuse turbidity with a flocculent sediment and much acid in dextrose ascites broth. It acidified but did not coagulate milk. It was not encapsulated and was bile insoluble. Rosenow stated that it resembles closely the organisms isolated from appendicitis and cholecystitis. His first cultures looked like staphylococci; there were no chains, and animal passage increased the size of the colonies and green production. There was no effect on mice following intraperitoneal injection. He found their fermentative powers extremely different, all fermenting dextrose, sucrose in fourteen of twenty strains, raffinose in eight out of fifty-two, mannitol in thirty-four of sixty, salicin in forty-six of fifty-five and inulin in three of sixty-four. He stated that the strains were not sufficiently alike to warrant considering them a distinct or specific species. A number of these cultures, however, were obtained from different sources than gastric ulcer. To produce ulceration in the duodenum of rabbits, Rosenow stated that, because of the low virulence of the strains, the intravenous dose was relatively large, consisting in the main of the growth of from 5 to 25 cc. of the broth culture per kilogram of weight. In special instances, much smaller doses sufficed to produce ulcer. Also, the selective affinity for the stomach and duodenum disappeared both after cultivation of the bacteria on artificial mediums for from one to six weeks and after animal passage, the incidence dropping from 60 to 0 per cent after cultivation and to 33 per cent after animal passage. Either or both hemorrhage and ulcer of the stomach or of the duodenum followed injection of all the strains from ulcer in a total of ninety-three animals, or 83 per cent. Either or both hemorrhage and ulcer followed injection of strains of streptococci

from sources other than ulcer in a total of ninety-nine animals, or 26 per cent. Rosenow sectioned the ulcers produced in dogs by Mann by the method of surgical duodenal drainage and found evidence of an infective process and the typical streptococcus. A culture of fresh tissue of one of the ulcers yielded a streptococcus which produced acute gastric and duodenal hemorrhages and ulcers in a high percentage of rabbits receiving injections, and few or no lesions elsewhere. In one of Durante's [6] chronic ulcers produced by ligating the splanchnic nerves, he also demonstrated not less than fifty cocci and diplococci in the depths of the tissues which showed leukocytic infiltration. A healed ulcer from the same stomach proved to be sterile, and tissue sections showed no evidence of leukocytic infiltration.

In 1909, Helmholz [31] reported twelve cases of duodenal ulcer in infants, aged from 1 to 6 months, which occurred during the last four months of 1908. In the first eight months of 1908 and the entire year of 1909, no further cases were observed by him. In ten out of fourteen ulcers from his first series and in all eight of the last series, diplococci were found in the ulcer base of tissue sections. A green streptococcus was isolated in one case. In 1915, Helmholz [32] again reported a series of eleven cases of duodenal ulcer in infants observed during the seven months from September to April. These were the only cases observed and "appeared to be an epidemic." In his series, he has demonstrated streptococci in all but four of fourteen ulcers. Rosenow was able to produce typical lesions in rabbits with the only strain isolated by Helmholz, and believed the organism identical to those he, Rosenow, had isolated.

Holt [33] and Veeder,[34] in their reviews of all cases of duodenal ulcer in children, reported in the literature (about 100 in all), showed that they occur in infants aged from 1 to 6 months, and only in marasmic infants with general lowered vitality.

In 1916 Celler and Thalheimer [35] isolated a nonhemolytic streptococcus from seven chronic ulcers removed at operation, using Rosenow's technic. The organism was described as a small gram-positive coccus forming short and long chains. The cultural characteristics of the organism were reported as almost identical with those of the strains isolated by Rosenow. With special stains, the organism was found only in or on the lining of the degenerating tissue but never in the depths. The chief organisms were minute cocci. These authors con-

31. Helmholz, H. F.: Arch. Pediat. **26**:661, 1909.

32. Gerdine, Linton; and Helmholz, H. F.: Duodenal Ulcer in Infancy an Infectious Disease, Am. J. Dis. Child. **10**:397 (Dec.) 1915.

33. Holt, L. E.: Duodenal Ulcer in Infancy, Am. J. Dis. Child. **6**:381 (Dec.) 1913.

34. Veeder, B. S.: Duodenal Ulcer in Infancy, Am. J. M. Sc. **148**:709, 1914.

35. Celler and Thalheimer: J. Exper. Med. **23**:791, 1916.

cluded that some cause is operative in certain cases, preventing the healing of defects in the gastric mucosa, and is inoperative in others. Even though a nonhemolytic streptococcus is present in practically all gastric ulcers, they did not believe that it had been proved to be a factor that either initiated ulceration or prevented healing. They were unable to reproduce the lesions in the stomachs of rabbits as Rosenow had done. They made no attempt to identify their strains serologically. In 1918, McMeans [36] stated that he was unable to support Rosenow [7] in the view of elective affinity. He produced experimental bacteremia in rabbits following the intravenous injection of various organisms obtained from different sources and observed with equal frequency hemorrhages and erosions in the stomachs of rabbits inoculated in this way. The organisms used were obtained from foci of infection in patients with ulcer. In 1923, Rosenow [7] stated that he believed the streptococcus of gastric ulcer produced a poison within its substance and free in broth cultures which injured the mucous membrane of the stomach. By immunizing one group of rabbits to ulcer strains and another group to encephalitis strains of streptococci and then making injections into all the rabbits with vulnerable doses of living ulcer-forming streptococci, he found that ulcers did not form in the animals immunized to the ulcer strains, whereas they did appear in the control rabbits immunized to encephalitis strains, but because of the disproportion of animals receiving injections (twenty-three with ulcer vaccine and seven with encephalitis vaccine) no definite conclusion should be drawn.

In 1925, Haden [37] made cultures from the roots of the teeth of twelve patients suffering from gastric ulcer and obtained a nonhemolytic streptococcus. Fifty-three per cent of forty-five rabbits receiving intravenous injections of broth cultures of these organisms showed gross lesions of the stomach or the duodenum, while 7 per cent of 535 rabbits receiving injections of broth cultures from 191 control patients showed similar lesions. The lesion produced was usually hemorrhagic erosion of the duodenum and occasionally, small ulcers.

In 1925, Meisser [38] gave eighty-one rabbits injections with the streptococcus obtained from teeth foci of twenty-two patients with ulcer and obtained hemorrhagic lesions of the stomach in 67 per cent. In 1925, Alban Girault [39] isolated a streptococcus from a gastric ulcer and made an emulsion (1,000 million to the cubic centimeter). This

36. McMeans, J. W.: Concerning the Gastric Lesions Observed in Experimental Bacteremia, Arch. Int. Med. **22**:114 (July) 1918.

37. Haden, R. L.: The Elective Localization of Bacteria in Peptic Ulcer, Arch. Int. Med. **35**:457 (April) 1925.

38. Meisser, J. G.: Further Studies on Elective Localization of Bacteria from Infected Teeth, J. Am. Dental A. **12**:554, 1925.

39. Girault, Alban: Arch. de mal. d. l'app. digestif **14**:924, 1924.

emulsion was used for skin sensitivity tests in patients with ulcer. It did not prove successful; so a small amount was injected deeply into the deltoid region of fourteen patients with proved gastric ulcer. Nine showed a positive reaction (tenderness, redness and swelling). Five showed a negative reaction. Duval, Roux and Moutier [40] stated that they had observed fever and leukocystosis (of 7,000, 10,000 and 32,000 cells) in twenty-eight cases of proved ulcer. They isolated a streptococcus from four of nine ulcers. Razemon [41] studied thirty-one ulcers and found only six sterile lesions. Roux and Girault [42] stated that when an ulcer is due to a streptococcus, vaccine therapy is indicated but that there is the danger of causing hemorrhage or perforation of the ulcer. They did not believe that ulcer was always due to a streptococcus, saying, "Sur un maladie à evolution aussi irregulaire que l'ulcère gastrique," and that vaccine therapy would benefit only those cases due to the streptococcus. Pierre Delbet believed that infection plays a large rôle in gastroduodenal ulcer and has successfully given a vaccine of pyocyaneus, coli, etc., to stop gastric hemorrhages. In 1925, Ivy and Shapiro [43] obtained necrosis, sloughing and healing of the gastric mucosa in from twenty-one to thirty days, in previously sensitized dogs following the injection of egg albumin, beef protein, etc.

In 1928, Nickel and Hufford [44] studied eighty consecutive cases of gastric ulcer, eighteen of which were of recurring and sixty-one of primary ulcer. One hundred and three strains of green-producing streptococci were obtained from various foci of the sixty-one cases of primary ulcer. Lesions of the stomach and duodenum were obtained in 63 per cent of the rabbits receiving injections of these strains. The foci included teeth, tonsils, prostate and cervix. Thirty-four strains were isolated from the foci of eighteen patients suffering with recurring ulcer, and lesions were produced in 71 per cent of the animals receiving injections. A green-producing streptococcus was isolated from ten resected gastric ulcers. In twenty-eight of thirty-one rabbits receiving injections of these ten strains, lesions resulted. Nickel stated that the green-producing streptococcus isolated was morphologically and according to sugar reactions indistinguishable from other green-producing strains which were isolated in arthritis, myositis and other conditions. He concluded that the causative streptococcus has been demonstrated in and isolated from the resected ulcer of man as well as from the

40. Duval; Roux and Moutier: Rôle de l'infection dans l'evolution des ulceres gastroduodenaux, Presse méd. **33**:3, 1925.

41. Razemon, quoted by Duval, Roux and Montier.

42. Roux and Girault: Arch. d. mal. de l'app. digestif. **15**:949, 1925.

43. Ivy, A. C., and Shapiro, P. F.: Experimental Production of Gastric Ulcer by Local Allergy, J. A. M. A. **85**:1131 (Oct. 10) 1925.

44. Nickel, A. C., and Hufford, A. R.: Elective Localization of Streptococci Isolated from Cases of Peptic Ulcer, Arch. Int. Med. **41**:210 (Feb.) 1928.

foci of infection and has produced electively similar lesions of the stomach and duodenum when injected intravenously in rabbits.

No cultural or serologic identity tests were attempted, without which one could not possibly conclude that the green-producing streptococcus obtained from gastric ulcer, teeth, tonsils, prostate and cervix are one and the same organism.

Nickel's technic in producing lesions in rabbits was to inject freshly isolated broth cultures, approximately eighteen to twenty-four hours old, in the marginal vein of the rabbit's ear; the dosage varied from

TABLE 1.—*Sources of Single Colony Strains from Stomach* *

Patient	Hospital	Ulcer	Single Colony Strains				Surgeon
1	Second Surgical, Bellevue	Large gastric, lesser curvature	1 A′ 2 A	3 A 4 A			Santee
2	Second Surgical, Bellevue	Small gastric, lesser curvature	19 AA′ 20 A	21 AA′ 22 A			Santee
3	Second Surgical, Bellevue	Small gastric, lesser curvature	23 A 23a A	23b A 23c A	23d A 23e A		Santee
4	Second Surgical, Bellevue	Malignant ulcer, midstomach	45 A 45a A	45b A 45c A	45d A 45e A 45f A		Santee
5	Mount Sinai, no. 300520	Duodenal	46 A 46a A	45b A			Berg
6	Mount Sinai, private patient	Large gastric Lesser curvature	47a A I II	Piece from surface of ulcer	47b A I A II A III A IV A V A VI A	whole section	Berg
7	Mount Sinai, no. 300854	Large gastric, lesser curvature	53 A 53a A	53b A 53c A	53d A		Berg
8	Second Surgical, Bellevue	Gastrojejunal duodenal still present; no growth	55 A 55a A	55b A 55c A	55d A		Dudley
9	Second Surgical, Bellevue	Gastrojejunal duodenal still present; no growth	56 A	56a A			Dudley
Strain from patient 2 injected into dog's stomach, strain recovered twenty-five days later			9 A 9a A	9b A 9c A			

* In this table and in the other tables, A indicates alpha; A′, alpha-prime; AA′, alpha-alpha-prime, and B, beta.

2 to 12 cc., depending on the size of the rabbit and the density of the culture. This injection was repeated once or twice with rapidly made subcultures, depending on the condition of the rabbit.

BACTERIOLOGIC AND SEROLOGIC REPORT

Streptococcal Types Isolated and Studied.—The sources from which the single colony strains, isolated from the multiple lesions and foci, were obtained are shown in the following tables (table 1).

There were forty-six single colony strains of streptococci isolated from nine resected gastric, duodenal and gastrojejunal ulcers cultivated immediately on resection at the operating table. Four single colony strains were recovered from the submucosa of a dog's stomach twenty-

five days after the injection of culture no. 2 into it. Forty-seven were alpha, two alpha-alpha-prime [45] and one alpha-prime strains.

Table 2 includes nineteen single colony strains which were isolated from five patients suffering from an acute disease characterized by fever and toxicity, presenting small punched out ulcers of the lip, tongue, tonsils and buccal membranes. In two patients, the condition became chronic with ulcerations of the tonsils and posterior pharynx; one

TABLE 2.—*Source of Single Colony Strains from Throat*

Patient	Ulcer	Single Colony Strains			
10	Throat	29 A	29b AA′	29d AA′	
		29a A	29c AA′		
11	Throat	32 A	32b A	32d A	
		32a A	32c A		
12	Lip and throat	37 A′	38 A		
13	Throat	39 A	39b B		
		39a A			
14	Throat	44 B	44b B		
		44a A	44c A		

TABLE 3.—*Source of Single Colony Strains from the Teeth*

Patient	Ulcer	Single Colony Strains			Teeth Foci
15	Duodenal	12 A			
16	Gastric	13 A			
17	Gastric	14 A			
18	Small gastric	15 AA′			
		16 A			
19	Small gastric	17 AA′			
		18 AA′			
20	Duodenal	28 A	28b A		
		28a A	28c G		
21	Duodenal	33 G	33b G		33d AA′
		33a G	33c G		
22	Duodenal	34 G	34b G		
		34a G			
23	Duodenal	35 G	35b G		
		35a G			
24	Hand—put wound to mouth repeatedly	27 A	27b A		
		27a A	27c A		
25	Died from Ludwig's angina	25 AA′	25b AA′		25d A′A
		25a AA′	25c A		

patient recovered in about two months; the other left the hospital acutely and critically ill, with beginning disease of the vocal cords and could not be followed, and in three the condition cleared up spontaneously in from ten days to two weeks. Twelve strains were alpha, three alpha-alpha-prime, one alpha-prime and three beta.

Table 3 shows thirty-one single colony strains which were isolated from foci in the teeth of nine patients suffering from gastric and duodenal ulcers, and one patient who had repeatedly put a skin wound

45. The term alpha-alpha-prime is explained later in the article.

of his hand to his mouth, thus causing an ulcer of the hand. Twelve were alpha, eight alpha-alpha-prime and eleven gamma strains. Streptococci obtained from the teeth of a patient who died with Ludwig's angina were also included in this series.

Table 4 shows eighteen single colony strains isolated from seven ulcers of the skin, lip or mouth due to traumatic injury causing the penetration of a tooth (human bite ulcers). This type of ulcer should not be confused with the human bite ulcer due to spirochetes and fusiform bacilli reported in the literature. Twelve were alpha-prime, three alpha-alpha-prime and three alpha strains.

TABLE 4.—*Source of Single Colony Strains from the Skin, Lip and Mouth*

Patient	Hospital	Ulcer	Single Colony Strains	
26	Second Surgical Clinic, Bellevue	Penetration of dorsum of hand by a tooth	5 A′	6 A′
27	Second Surgical Clinic, Bellevue	Lip; tooth pierced upper lip	7 A′	8 A′
28	Second Surgical Clinic, Bellevue	Hand; put wound to mouth repeatedly	11 A′	
29	Second Surgical Clinic, Bellevue	Penetration of dorsum of hand by a tooth	26 A a AA′ b AA′	c A d AA′
30	Second Surgical Clinic, Bellevue	Penetration of dorsum of hand by a tooth	30 A′ 30a A′	30b A′
31	Second Surgical Clinic, Bellevue	Lip; loss of lower lip by penetration of own teeth	31 A′ 31a A′ 31b A′	31c A′
32	Second Surgical Clinic, Bellevue	Lip; injury to lower lip	40 A	

TABLE 5.—*Miscellaneous Single Colony Strains*

Patient	Hospital		Single Colony Strains
33	Second Surgical, Bellevue	Streptococcus	43 B
34	Second Surgical, Bellevue	Erysipelas	41 B
35	Second Surgical, Bellevue	Empyema of thoracic cavity	42 B

Table 5 shows three single colony strains which were isolated from three patients suffering from streptococcus gangrene, erysipelas and empyema of the thoracic cavity, respectively. These three were beta strains and were used for comparative purposes.

This makes a total of 117 single colony strains of streptococci, from which the strains used for the cultural and serologic investigation were chosen. Direct smears for spirochetes, fusiform bacilli, yeast and the Klebs-Loeffler bacillus were repeatedly reported negative by more than one observer in each of the four cases reported in table 2.

In four cases of ulcer of the stomach streptococci were not recovered. Two of these were jejunal ulcers, and only the platinum loop could be pressed into the crater, a piece of tissue not being available. Three were duodenal ulcers, two in the same patient, who had had a previous

gastro-enterostomy and in whom gastrojejunal ulcers were present. The duodenal ulcers showed signs of healing but still were present. Cultures from these were sterile after ten days at incubation temperature.

A piece of duodenal mucosa from a patient operated on for ulcer but presenting duodenitis was likewise sterile. *Micrococcus gazogenes*, a minute gram-negative diplococcus, an obligatory anaerobe, was the only organism grown from a large gastric ulcer on the lesser curvature in the midportion of the stomach. This organism has been described by Hall [46] as occurring in the flora of the mouth and also by Noble. Normal mucosa of the stomach gave repeatedly sterile cultures except for one case in which a gamma enterococcus was grown. The alpha streptococcus was obtained in pure culture from five ulcers and mixed with either *B. welchii*, *B. coli*, a gamma enterococcus or a peculiar staphylococcus in four. A culture was obtained from a case of empyema of the gallbladder, one of an acute suppurative appendix and one of peritonitis, the result of a perforated duodenal ulcer of one day's duration. The alpha streptococcus was not obtained from any of these. A gamma streptococcus (enterococcus), staphylococcus and morphologically varying bacilli were the organisms recovered.

Technic.—Cultures from all ulcers of the stomach were taken in the operating room immediately on resection. Small pieces of the ulcer, about 0.25 cm. in diameter, were cut out aseptically and with a platinum loop placed into a tube containing about 15 cc. of 0.5 per cent semisolid hormone agar medium (Huntoon) with a reaction of p_H 7. When the platinum loop was heated slightly, the tissue could be readily carried to the bottom of the tube. From six to eight cultures were made from each ulcer, pieces of tissue from different areas and different depths of the ulcer being used; the pieces were washed in sterile saline solution in some cases and not in others. Cultures from pieces of normal stomach wall were made in the same manner. The first ulcer was cultivated anaerobically in a kidney and serum medium and sealed with petrolatum. It was incubated for twenty-five days before examination. A streptococcus was the only growth obtained, except for a few large gram-positive bacilli; after plating, the streptococcus colonies were transferred to the semisolid hormone agar. They grew so well in this medium that all cultures were taken directly into it thereafter. There was never any growth at the top of the stab culture unless contaminants were present. The organism grew profusely in the depth of the stabs. This method seemed simpler than Rosenow's method in which tall ascites-dextrose-agar tubes are used to obtain the right oxygen tension and was apparently as effective. At the end of twenty-four hours, there was usually no growth. The tissue would then be stirred up with a sterile platinum loop. This was repeated at the end of each twenty-four hours until growth appeared, or up to ten days if the culture remained sterile. Growth usually appeared in from three to six days. As soon as growth appeared, which was always adjacent to the tissue, it was transferred to other semisolid hormone agar tubes, incubated for twenty-four hours and then placed in the icebox. It was noted that the tubes

46. Hall, I. C.: The Anaerobic Bacteria of the Oral Cavity, Proc. Soc. Exper. Biol. & Med. **22**:541, 1925.

containing the largest pieces of tissue were usually the sterile tubes. It was felt that the tissue possibly contained a bactericidal substance that prohibited growth. For this reason, small cut sections were used. Wilkie [47] found this true in cultures made from lymph glands. If contaminants appeared on the surface of the agar, the tube was cracked by filing circularly 1 cm. below the surface of the agar and applying a red hot end of a file to the groove; this would crack the tube evenly. The piece of tissue and deep solid mediums were then transferred to a sterile petri dish, and either the growth or the tissue transferred to another tube of semisolid agar. This proved to be a time-saving and efficient procedure and was devised by Dr. Kahn. The first growth in the hormone agar was immediately surface seeded on two bromcresol purple lactose agar plates. After from twenty-four to forty-eight hours' incubation at 37 C. from six to eight single, well isolated, similar streptococcal colonies were then fished into semisolid hormone agar tubes. After forty-eight hours' incubation, each culture was streaked on a plain blood agar plate (p_H 7.4) for purity of culture and effect on the medium, and the observations were recorded at the end of twenty-four hours and forty-eight hours. The plates were then left in the icebox for four or five days when the degree of hemolysis, if present, was increased. Transplants of each purified stock culture were made every three weeks, that being considered the limit of safety.

Cultures from the teeth were made directly with the platinum loop, after the mouth was cleansed, from the pockets between the teeth and the gums; the patients in every case had marked pyorrhea so that the platinum loop could be forced to the bottom of the tooth socket. These were planted directly into the semisolid agar. These tubes could be cracked in twenty-four hours, the surface growth which was always profuse, discarded, and the growth from the bottom transplanted. The growth was then carried through in the same manner as that described for the ulcer strains.

Haden,[37] Nickel [9] and Meisser [38] obtained the streptococcus from teeth after extraction by cleansing and putting the apex of the tooth, cut off with sterile nippers, into the culture medium. By this method, a different streptococcus may possibly have been obtained.

The ulcers of the skin and lip caused by human bites always had a creeping, dissecting edge. After cleansing the surface, the platinum loop could be forced under this dissected edge. In the majority of these cases the streptococcus was the only growth, so that the tubes did not have to be cracked. The experiment was then carried on in the same manner.

Cultures were obtained from the four specific acute cases of ulcers of the lip, the tongue, the buccal membranes and the tonsils by cleansing the mouth and applying the platinum loop as in the ulcers of the skin caused by human bites. With these cultures, contaminants were rare.

For experimental inoculations into animals, the procedure consisted of direct injection into the stomach wall of twenty-four hour dextrose broth cultures (p_H 7.4). The growth was decidedly less in plain broth. For intravenous injections into rabbits, the saline washings of the twenty-four hour growth on 0.5 per cent hormone agar slant were used.

The sections cut for Levaditi stains were fixed in 10 per cent neutral solution of formaldehyde immediately on resection.

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47. Wilkie, A. L.: The Bacteriology of Cholecystitis, Brit. J. Surg. **15**:450, 1928.

The Morphology of the Alpha Streptococcus.—The organism varied markedly, depending on its age and the mediums on which it was cultivated. The first ulcer in the stomach had been cultivated anaerobically in serum kidney broth sealed with petrolatum for three weeks. Direct smears from this growth showed short chains of diplococci. The individual diplococci appeared large and lanceolate in shape and showed many large, involuted forms. The growth on a blood plate from the original culture showed two different types of colonies, one a small discrete grayish-white colony producing a faint hemolysis, the other colony not showing any hemolysis but definite greening. On staining, both colonies appeared the same. These colonies when transferred to dextrose broth and cultivated for two or three days at incubation temperature showed a varying size of lanceolate gram-positive diplococci in short and long chains. Some appeared distinctly as rods or fused cocci resembling rods and short bacilli (fig. 1, *B*).

All of the direct original cultures on semisolid hormone agar appeared morphologically the same on first growth, that is, lanceolate cocci often fused together as short rods (fig. 1, *A*).

It would be impossible to say from the morphologic aspect alone that cocci and bacilli were not present; however, when this primary growth was passed through dextrose broth only long and short chains of lanceolate cocci would be present, varying distinctly in size and shape (fig. 1, *B*).

The first three cultures when streaked on plain meat infusion blood agar plates (p_H 7.4) were read as alpha prime streptococci after forty-eight hours at incubation temperature. However, when they were again put on these blood agar plates after artificial cultivation, there was no sign of hemolysis and only slight greening on the surface, but marked greening when the inoculated loop was penetrated into the medium. Some few colonies showed the faintest possible zone of hemolysis which would again be lost on further artificial cultivation.

After a gastric strain, culture 23, was approximately 5 months old and was in its tenth generation and had been in the icebox for ten days, a twenty-four hour dextrose broth culture was made. This culture well diluted was seeded on plain and dextrose meat infusion blood agar plates (p_H 7.4) and incubated at 37 C. A twenty-four hour reading showed equal growth on both plates of equal sized colonies about 0.5 mm. in diameter with irregular edges and a rough surface. There was markedly more greening on the dextrose blood plate, but the strain was not definitely glycophilic. A forty-eight hour reading was practically the same, except for a slight increase in size to from 0.75 to 1 mm. in diameter. The colonies were extremely adherent to the medium. This culture was also put on whey agar, p_H 5.8, on which *Streptococcus fecalis* grows well, but there was no growth of this organism in forty-eight hours.

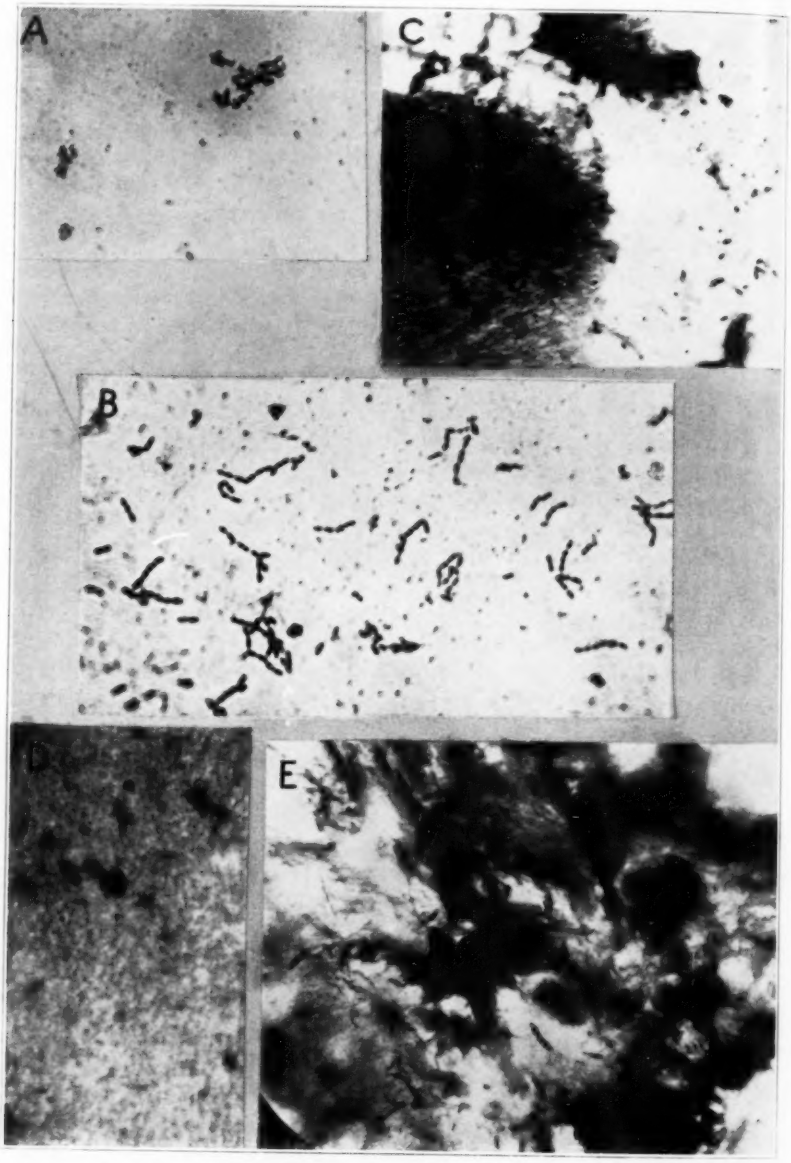

Fig. 1.—*A*, the morphologic appearance of the original growth of gastric streptococcus from ulcer tissue in 0.5 per cent hormone agar, showing no chains, but bacilloid and fused cocci forms clumped together. *B*, chaining together of lanceolate diplococci forms with some bacilloid forms after artificial cultivation. *C*, bacilloid and diplococcic forms in the necrotic surface of an ulcer. Levaditi tissue section. *D*, diplococci forms in the necrotic exudate below the surface of the ulcer. Levaditi tissue section. *E*, Levaditi tissue section from a granuloma at the base of a tooth after extraction, showing many spirochetes and fusiform bacilli, but no diplococci.

Heat resistance of this culture had previously been tested when it was in its first generation along with two other cultures in their first generation, namely, 2 and 19. Twenty-four hour cultures in plain nutrient broth (p_H 7.2) were heated in narrow tubes to 60 C. for fifteen minutes and then tested for sterility by streaking on agar plates. The organisms were not killed but grew out profusely in twenty-four hours. It was again tested on the present (tenth) generation, being heated in milk tubes to 65 C. for twenty minutes, which is slightly above the heat used in pasteurization processes and which is considered sufficient to kill all nonspore-bearing pathogenic organisms within thirty minutes in commercial processes. The heated culture was then streaked on cresolpurple lactose agar plates, but there was no growth after forty-eight hours' incubation. This may be due to its slightly lowered resistance, the result of artificial cultivation. The organism grew slightly more profusely in dextrose broth than in plain broth. The growth in semisolid hormone agar stabs was profuse, granular and discrete along the entire line of the stab. There was never any growth spreading over the surface. Rosenow [7] and Nickel [1] stated that the streptococcus cultivated from gastric ulcer would sometimes occur in irregular clumps and in tetrads and quatrads. The fused cocci resembling rods were frequently clumped together in the original growth but tetrads and quatrads were noted only in the peculiar staphylococcus contamination in the cultures.

Morphologically, the alpha and alpha-prime strains from foci in the mouth and human bites were practically the same as the gastric strain except that cocci were usually more round and rarely were definitely lanceolate. The first growth on a blood plate of one of the strains from an ulcer of the lip, cultures 37 and 38, which was one of the acute cases shown in table 2, was identical with a pneumococcus colony. However, on staining, long chains of gram-positive lanceolate streptococci were present. Rosenow [7] claimed the transmutations of streptococci and pneumococci in 1916. It has been repeatedly observed that strains gain or lose hemolysis on artificial cultivation. This department is certain that the strains are recorded correctly and felt that it was desirable to call an unusual strain, faint hemolysis of which persisted, an alpha-alpha-prime. The hemolysis was not sufficient to term it an alpha-prime. This does not fall in with the accepted terminology (Brown) but is readily understood. This streptococcal type which is here reported as having been isolated from nearly 100 per cent of gastric, duodenal or gastrojejunal ulcers should therefore be termed a nonhemolytic streptococcus of the alpha type.

Fermentation and Other Cultural Tests.—The basal medium employed was semisolid (0.5 per cent) meat extract, 1 per cent peptone

agar, p_H 7, tinted with bromcresol purple as indicator. The sugars were added in 1 per cent strength for lactose, sucrose, salicin and inulin and 0.5 per cent for raffinose and esculin. Proper precautions were taken in sterilization. The fermentation reactions were recorded after four days' incubation at 37 C.

The single colony strains chosen for serologic work were put through seven sugars to determine fermentative reactions, with the following results: Eight of the ten type strains from ulcers of the stomach fermented lactose, sucrose and salicin, but did not ferment mannitol, raffinose, inulin or esculin. The other two strains fermented no one of these sugars by the method used. The five throat strains of table 2 also fermented lactose, sucrose and salicin and no other sugars, with the exception of one which fermented raffinose. Seven cultures obtained from ulcers on the hand, lip and mouth fermented lactose, sucrose and salicin but did not ferment mannitol, raffinose, inulin or esculin. Of the eleven strains isolated from the teeth or mouths of patients suffering from gastric ulcers, four different reactions were obtained with these test sugars. Two fermented lactose, sucrose and raffinose. Four fermented lactose, sucrose and salicin. Four fermented lactose and sucrose, and one fermented sucrose and mannitol. The gangrene strain fermented lactose, sucrose, salicin, mannitol and esculin; the erysipelas strain, salicin and mannitol. The strain obtained from the empyema of the thoracic cavity fermented sucrose and salicin. These three were beta strains. In the failure of the ulcer streptococcal strains to split mannitol and esculin, the relationship to mouth and throat types rather than to intestinal types is indicated.

These results, as will be seen later, indicate that the serologically identical organisms have the same fermentative reactions in practically 100 per cent and that those unrelated, serologically, are markedly heterogeneous.

An attempt was made to see whether the gastric streptococcus would grow in 0.5 per cent hormone agar acidified to the acidity of the stomach. Five tubes were made up with a hydrochloric acid content ranging from 0.5 to 0.1 per cent, respectively. Control tubes were also prepared with from 0.5 to 0.1 per cent sodium hydroxide content, respectively. The eleventh tube had a reaction of p_H 7.4. Growth occurred in the 0.1 and 0.2 per cent acid tubes and in the 0.1 and 0.2 per cent alkaline tubes. There was no growth in the 0.3, 0.4 and 0.5 per cent tubes of both acid and alkali. The growth in the control tube, p_H 7.4, was profuse. Therefore, the gastric streptococcus probably has not a special ability to grow in strongly acid medium. The gastric streptococcus does not grow in bile; gelatin is not liquefied after ten days, but milk is almost completely clotted. This is interesting because of the directly opposite results of others.

COMMENT

Morphologically and culturally, the nonhemolytic streptococcus isolated by certain other investigators (Rosenow, Nickel, Celler and Thalheimer) would seem to be identical with that recovered in this investigation. However, no agglutinogenic or antigenic studies have previously been made, and there is no certainty of specific relationship. When one reviews carefully the work of Krumwiede [48] in 1916 and that of Hooker [49] and his co-workers in 1929, the marked heterogeneity of the alpha type is convincingly proved. Hooker concluded that in the alpha type cross-agglutination and fixation tests have demonstrated a bewildering antigenic heterogeneity. He observed strong cross-agglutination in less than 3 per cent of 616 tests. No identical strains from different sources were discovered when a total of 2,057 colony strains were studied from 101 specimens. Group reactions occurred among fermentative heterologs as well as among strains of the same fermentative type. Antigenic unlikeness also features the identical colony strains derived from one individual.

It is therefore impossible to believe that alpha strains from such a wide variety of sources, such as teeth and tonsils and prostatic and cervical foci, could possibly be agglutinogenic and antigenic homologs or show a specific relationship with the gastric strain. One needs only to read Krumwiede or Hooker's review of the literature for evidence as to the homogeneity or heterogeneity of an individual's strains of streptococci to be convinced that all careful observations have consistently proved the extreme heterogeneity of the alpha type.

AGGLUTINATION INVESTIGATION

The following results show that the nine alpha strains from ulcers of the stomach are agglutinogenic and antigenic homologs and that they are identical with four other strains isolated from an acute specific disease. The tables also show the agglutinogenic and antigenic unlikeness to all the other strains, although some of these produce similar pathologic lesions, others, foci of infection, and all are culturally and morphologically similar.

Technic of Streptococcic Agglutination; Preparation of Immune Serums.—The growth from a twenty-four hour slant of hormone agar suspended in 1 cc. of saline solution is injected intravenously into rabbits without killing the organisms by heat or a chemical. On the first day, 0.2 cc., the second day, 0.4 cc., the third day, 0.4 cc., and on the fourth day, 0.6 cc., were injected. If the rabbit loses more

48. Krumwiede, C.: A Study of the Agglutination and Cultural Relationship of the So-Called Streptococcus-Viridans Group, J. Infect. Dis. **19**:760, 1916.

49. Hooker, S. F., and Anderson, L. M.: Heterogeneity of Streptococci Isolated from Sputum, with a Critique on Serological Classifications of Streptococci, J. Immunol. **16**:291, 1929.

than 50 Gm., the dose of the previous day is repeated. If the animal loses more than 100 Gm., no dose is given. After three days' rest, the rabbit is again inoculated for four days as follows: first day, 0.8 cc., second day, 1 cc., third day, 1.2 cc. and fourth day 1.4 cc. After a week a trial bleeding is made, and if the serum is of the proper titer the rabbit is bled to death. Otherwise, the second week's dosage is repeated.

Preparation of Antigen.—The strain of streptococcus is cultivated by daily replants in beef heart infusion peptone broth plus 2 per cent of sodium diphosphate and 0.1 per cent dextrose until a homogeneous growth suspension is obtained. If this suspension stays up overnight at 55 C. in this phosphate broth minus dextrose, the antigen is ready for use and can be made up in larger quantity. This is done by planting this homogenized culture in 200 cc. of dextrose broth, growing over night, washing three times in the aforementioned medium without dextrose and resuspending in phosphate broth to the proper concentration, which is about 3 billion per cubic centimeter. Solution of formaldehyde, 0.2 per cent is added, but no heat is used.

Technic of Set-Up: One-tenth cubic centimeter of the following dilutions is put in each of eight tubes:

Tube 1 1-10	Tube 4 1- 80	Tube 7 1- 640
Tube 2 1-20	Tube 5 1-160	Tube 8 1-1280
Tube 3 1-40	Tube 6 1-320	Tube 9 Saline solution and antigen

Nine-tenths cubic centimeter of antigen is added to each of these tubes, making a dilution of 1 : 100 in the first tube, 1 : 200 in the second tube, etc.

The tubes are left in the water-bath at 55 C. over night and a reading taken, the following symbols being used:

++ indicates complete agglutination—fluid clear.
+1, nearly complete agglutination—slightly cloudy and fluid clumps smaller.
+, 50 per cent complete.
±, slightly less than 50 per cent.
1, trace of agglutination.

Technic of Absorption.—The absorbing dose is the smallest dose of culture which when added to a certain amount of antiserum under suitable conditions will absorb all of its agglutinins. Testing with doses of 1 : 4, 1 : 10, 1 : 20, 1 : 30 and 1 : 40 usually covers the range of absorption. To test the absorptive capacity of other cultures, twice the volume is used. Broth cultures are centrifugated in accurately calibrated centrifuge tubes until the organisms are tightly packed. The amount is noted and the supernatant fluid decanted. Ten per cent is subtracted from the original reading, as all the broth cannot be poured off. The volume of cells is then multiplied by the absorbing dose which gives the total fluid to be used. This number minus the volume of organisms and divided by the serum dilution of 1 : 10 will give the amount of serum to be added. For example, using 0.4 cc. of packed cells and an absorptive dose factor of 10.

$$0.4 - 0.04 = 0.36 \times 10 = 3.6 - 0.36 = 2.24 \div 10 = 0.224$$

The 0.224 cc. of serum is added and the salt solution added to 3.6 cc.

The cocci are thoroughly mixed with diluted serum and placed in the water bath at 45 C. for two hours, being shaken at fifteen minute intervals. Tubes are then left in the icebox over night to complete absorption and centrifugated to clarify diluted serum. This serum is then used for agglutination tests with the

same dilutions used in the original test. Untreated diluted serum is carried through the same way as a control against the determination. This absorptive technic is modified after that of Dr. Anna Williams.

TABLE 6.—*Agglutination Data.*

Antigens	Serum 2	Serum 46	Serum 47	Serum 9	Serum 29	Serum 40
Gastric 2	6,400	3,200	6,400	6,400	6,400	800
Gastric 20	3,200	6,400	4,800	4,800	4,800	.....
Gastric 23	6,400	6,400	6,400	6,400	4,800	.....
Gastric 45	3,200	3,200	3,200	6,400	4,800	.....
Gastric 46	6,400	6,400	6,400	6,400	6,400	.....
Gastric 47	4,800	3,200	6,400	6,400	6,400	.....
Gastric 53	6,400	3,200	3,200	4,800	3,200	.....
Gastric 55	3,200	3,200	4,800	4,800	3,200	.....
Gastric 56	3,200	3,200	6,400	6,400	3,200	.....
Dog, gastric 9	3,200	6,400	6,400	6,400	3,200	.....
Throat 29	6,400	3,200	6,400	3,200	6,400	.....
Throat 38	3,200	3,200	3,200	3,200	3,200	.....
Throat 39	4,800	3,200	3,200	3,200	6,400	.....
Throat 44A	3,200	3,200	3,200	3,200	3,200	.....
Mouth 15	200	100	200	200	100	800
Mouth 17	0	0	0	0	0	600
Lip 31	0	0	0	0	0	800
Lip 40	0	0	0	0	0	3,200
Lip 7	0	0	0	0	0	1,200
Hand 11	0	0	0	0	0	800
Hand 30	0	0	0	0	0	600

TABLE 7.—*Data of Agglutination and Absorption*

Agglutination with Serum 2

Antigens	1:100	1:200	1:400	1:800	1:1,600	1:3,200	1:6,400	1:12,800	Control
Gastric 2	++	++	++	++	++	+1	+	±	—
Gastric 20	++	++	++	++	++	+	±	1	—
Gastric 23	++	++	++	++	++	+1	+	±	—
Gastric 45	++	++	++	++	++	+	±	1	—
Gastric 47	++	++	++	++	++	+1	±	±	—
Gastric 53	++	++	++	++	++	+1	+	1	—
Gastric 55	++	++	++	++	++	+	±	1	—
Gastric 56	++	++	++	++	++	+	±	1	—
Gastric 9	++	++	++	++	++	+	±	—	—
Throat 29	++	++	++	++	++	+1	+	1	—
Throat 38	++	++	++	++	++	±	±	1	—
Throat 39	++	++	++	++	++	+1	±	1	—
Throat 44A	++	++	++	++	++	+	±	1	—

Absorption of Serum 2

Antigens	1:100	1:200	1:400	1:800	1:1,600	1:3,200	Control
Gastric 2	—	—	—	—	—	—	—
Gastric 20	—	—	—	—	—	—	—
Gastric 23	—	—	—	—	—	—	—
Gastric 45	—	—	—	—	—	—	—
Gastric 46	—	—	—	—	—	—	—
Gastric 47	—	—	—	—	—	—	—
Gastric 53	—	—	—	—	—	—	—
Gastric 55	—	—	—	—	—	—	—
Gastric 56	—	—	—	—	—	—	—
Gastric 9	—	—	—	—	—	—	—
Throat 29	—	—	—	—	—	—	—
Throat 38	++	+	1	—	—	—	—
Throat 39	—	—	—	—	—	—	—
Throat 44A	++	++	+	±	—	—	—

The agglutination and absorption tables are self-explanatory. Agglutination has been recorded in table 6 up to the point of 50 per cent agglutination. It will be noticed in table 7 that less than 50 per cent agglutination and a trace extends out to the highest titer 12,800 in practically all identical organism strains. There was slight agglutina-

tion in the absorption test of one of the throats, no. 39, recorded in table 8. This culture was obtained one week after the onset of the infection, and it had subsided markedly. This may account for the slight dissimilarity. The culture from throat 44*A* gave more marked agglutination and is probably not identical. The report should therefore state that only four alpha strains from the throat are absolutely identical serologically with the gastric strains. It should be noted that, as shown by table 9, when serum 40, an alpha-prime strain from an ulcer of the lip, was set up against the antigens of the other alpha-

TABLE 8.—*Data of Absorptions*

Antigens	Serum 2	Serum 46	Serum 47
Gastric 2	0*	0	0
Gastric 20	0	0	0
Gastric 23	0	0	0
Gastric 45	0	0	0
Gastric 46	0	0	0
Gastric 47	0	0	0
Gastric 53	0	0	0
Gastric 55	0	0	0
Gastric 56	0	0	0
Gastric 9	0	0	0
Throat 29	0	0	0
Throat 38	0	0	0
Throat 32	0	0	0
Throat 39	200	200	100
Throat 44A	400	300	400

* The zeros indicate no agglutination, which proves identical organisms when the agglutinins have been absorbed.

TABLE 9.—*Data of Strain from Ulcer of Lip Caused by Penetration of Tooth.*

	Serum 40								
Antigens	1:100	1:200	1:400	1:800	1:1,600	1:3,200	1:6,400	1:12,800	Control
Lip ulcer 40	++	++	++	++	+1	+	±	1	—
Teeth 15	++	++	+1	+	1	—	—	—	—
Teeth 17	++	++	+1	±	—	—	—	—	—
Lip ulcer 31	++	++	++	+	1	—	—	—	—
Hand ulcer 7	++	++	++	+1	±	1	—	—	—
Hand ulcer 11	++	++	++	+	±	1	—	—	—
Hand ulcer 30	++	++	++	±	1	—	—	—	—
Gastric 2	++	++	+1	±	±	—	—	—	—

prime strains and also against the antigen of gastric strain 2, there was 50 per cent agglutination to approximately 1:800. Previously, when the gastric strain serum had been set up against the alpha-prime antigen there was no agglutination. This would tend to strengthen the proof that only the gastric strain is a specific one, but that the alpha-prime strain is related and can stimulate some agglutinins for it. Absorption tests were not done with the alpha-prime strains, but they would probably not be identical because of their much lower degree of agglutination, approximately the same as the teeth alpha strains, which certainly are not identical.

PATHOLOGY OF ULCER

It seems most interesting and unique that Cruveilhier,[17] one hundred years ago and thirty years before Pasteur and the discovery of the relation of micro-organisms to disease, should have described gastric ulcer as an inflammatory lesion typical of inflammation elsewhere; that Böttcher [23] in 1874, Gaillard [25] in 1882 and Letulle [24] in 1888 reported the presence of micro-organisms in stained tissue sections of gastric ulcer, that Sidney Martin [15] in 1895 felt that gastric ulcer was identical "avec la nécrose bacterienne." Since that time, the inflammatory character of ulcer and the presence of micro-organisms in stained sections of gastric ulcer have been reported many times. Most authors report the organism as a diplococcus. Since ulcers resected at operation have been available for tissue sections, much more accurate descriptions have been made. Askanazy,[50] in 1924, reported that there were four typical zones noted in the ulcer: (1) exudation, (2) fibrinoid necrosis, (3) granulation, and (4) cicatrization. According to Karsner,[51] the exudation may be purulent, sanguinopurulent, fibrinopurulent or catarrhal. Granulation tissue is variable in extent and is not different from granulation tissue elsewhere. It appears early in the course of the ulcer and is still present in large old ulcers. In many of the early ulcers, there is a fairly widespread acute gastritis which may be superimposed on the chronic hypertrophic gastritis, which in the experience of these authors accompanied a large number of ulcers of all stages. This fact has been noted repeatedly, and it is of interest to hear surgeons state that when a stomach is resected the gastric mucosa seen does or does not look like the mucosa seen when an ulcer is present. It is the typical l'état mamelonée, first described by Virchow in alcoholic gastritis, which is almost constantly found when ulcer is present. Karsner [51] concluded by saying that, pathologically, peptic ulcer is an inflammatory lesion so situated that gastric juice probably emphasizes the destruction of tissues, and that the inflammation is primary is suggested but is not proved. He deviated from his pathologic description to say that hyperacidity, stasis, whether of neuromuscular or obstructive origin, the irritative and traumatic influence of gastric contents and the traction of muscle about the ulcer are primary factors.

In 1923, after studying many sections of gastric ulcer, Stewart [52] stated that he believed that the most common cause of acute ulcer was bacterial infection.

50. Askanazy: Ueber Bau und Entstehung des chronischen Magengeschwürs sowie Soorpilz befunde in ihm, Virchows Arch. f. path. Anat. **234**:111, 1924; **250**:370, 1924.

51. Karsner, Howard T.: The Pathology of Peptic Ulcer, J. A. M. A. **85**: 1376 (Oct. 31) 1925.

52. Stewart: The Pathology of Gastric Ulcer, Brit. M. J. **2**:955, 1923.

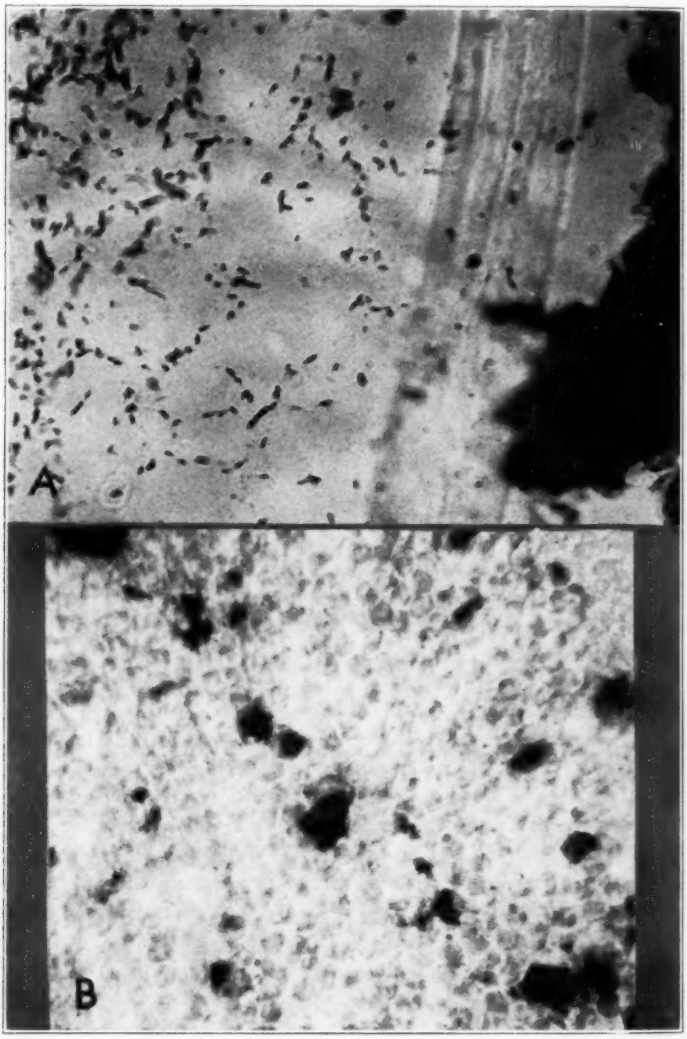

Fig. 2.—*A*, Levaditi tissue section of ulcer showing the destroyed surface covered with coccus and bacilloid forms which comprises the necrotic rim of the crater spoken of previously. *B*, Levaditi tissue section of ulcer showing sanguino-exudate with many degenerating phagocytic white cells.

McCarty [53] concluded from the pathologic study of material from 216 partial gastrectomies that, after the initial destruction of the mucosa, ulcers deepened by necrosis, and that the deepening was sufficiently slow to allow a definite dense connective tissue barrier against perforation to be formed.

Fig. 3.—Levaditi tissue section of ulcer showing the irregular destroyed glandular surface with many diplococci and bacilloid forms.

This department wishes to report its conclusions following the study of serial Levaditi sections of many gastric ulcers. Four are those in which the streptococcus was recovered in culture. Small pieces were cut immediately on resection in the operating room and fixed in 10 per cent neutral solution of formaldehyde. They were then carried

53. McCarty, N. C.: Pathological and Clinical Significance of Stomach Ulcer from the Study of Material from 216 Partial Gastrectomies, Surg. Gynec. Obst. **10**:449, 1910.

through and stained by the method of Levaditi. When fixed immediately in this manner, a rim of streptobacilli was always present covering the necrotic surface of the mucous membrane as shown in figure *2 A*. Single cocci, diplococci, streptobacilli and bacilli were constantly present in the purulent, sanguinopurulent, fibrinopurulent or catarrhal exudate which forms the surface of the ulcer, as shown in figure 3 and figure *2 A*. Phagocytic white cells showing large stained granules were numerous in the sanguino-exudate (fig. *2 B*).

The organisms were practically never found below the submucosal layer, and never in the muscular layers. If the base of the ulcer was a cicatrized muscle layer, the mucosa having been entirely destroyed, no organisms could be found. The glands of the mucosa adjacent to the exudative necrotic crater would invariably show organisms and beginning destruction. The mucosa not adjacent to the crater appeared normal, and the rim of organisms on the surface stopped.

It would appear, therefore, that the inciting organism attacks the mucosa directly, causing its destruction or necrosis, leaving a cicatrized or granulating base and never invading the muscular layers. It would be difficult to say or to prove by the morphologic appearance of the organisms in the Levaditi sections whether or not they are the streptococci recovered in culture. Some are definitely bacilli and morphologically appear as colon bacilli. The greatest number, however, resemble the first growth of the streptococci in hormone agar, that is, single and diplococci and fused cocci appearing as small bacilli or rods. Mouth spirochetes and fusiform bacilli were questionably present once or twice. It is this department's belief that the primary organism is the streptococcus, for it is always found in the most numbers and only infrequently associated with others. Its varying morphologic appearance can easily be accounted for when one sees its appearance on primary culture, changing markedly under artificial cultivation.

In 1928, Leriche[54] stated that gastric ulcer was a disease of the emptying stomach, not of the digestive stomach. He believed, therefore, that the type of gland in which the ulcer occurred should be investigated. Cogniaux,[55] therefore, examined 45 specimens and found that the ulcer occurred in the region of the pyloric glands 25 times, in the glands of Brunner 6 times, 9 times partly in pyloric and partly in duodenal, 3 times in pyloric and fundic and only 2 times in fundic glands alone. He believed, therefore, that in 95 out of 100 cases the ulcer occurs in the mucous secreting alkaline glands. His pathologic

54. Leriche, M. R.: Examen critique des idees sur le traitement des ulceres gastro-duodenaux, Bull. et mém. Soc. nat. de Chir. **55**:233, 1929.

55. Cogniaux: Sur le development presque exclusif des ulceres gastriques en milieu de glandes a mucus, Presse méd. **36**:589, 1929.

description is similar to those previously stated. He found that which has been stated many times before—that hypertrophic, atrophic and metaplasic gastritis accompanies ulcer.

Experimental Pathologic Conditions.—An attempt was made to reproduce an ulcer in the stomach of a dog by the direct injection into it of the alpha streptococcus recovered from a human gastric ulcer. In two dogs at laparotomy, 0.5 cc. of a twenty-four hour broth culture was injected directly into the muscular or submocosal layers of the lesser curvature just proximal to the pylorus with a syringe and small caliber needle. Sterile incubated broth was injected just proximal to this. Cultures 2 and 3 were used. Twenty-five days later the dogs

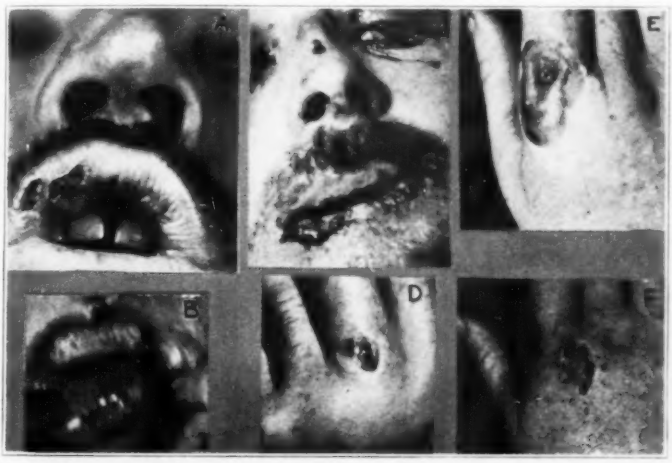

Fig. 4.—*A*, ulcer of upper lip following penetration of a tooth. Culture strain 7 and 8. *B*, ulcer of lower lip following penetration of tooth. Culture strain 40. *C*, complete loss of lower lip following blow in the mouth and complicated erysipelas. Culture strain 31. *D*, ulceration of knuckle joint following repeated contact of small abrasion with mouth. Culture strain 30. *E*, superficial ulceration extension only involving dermis following penetration of tooth. Culture strain 26. *F*, ulcer of knuckle following penetration of tooth. Culture strain 5-6.

were reoperated on, and that area of the stomach excised, examined and cultures made. The muscular layers were greatly thickened; the overlying mucosa was slightly blue; the site of injection of sterile broth could not be differentiated from the normal stomach wall, and there was no ulceration of the mucosa underlying the site of injection. The organism was recovered from the site of injection of culture 2.

At operation, before an attempt was made to excise this area, the most rigid reverse peristalsis coming up the duodenum and extending

on the stomach only to the site of injection occurred. It was a most remarkable rigid contraction and occurred about every half minute, lasting from fifteen to twenty seconds. It seemed quite logical to assume that if this were a common occurrence it could well explain pain and the inability of an ulcer to heal.

It was felt that the organism would have to be injected directly into the mucosa, for when injecting through serosa one could not be sure of the exact layer into which the injection was going. Injection of a twenty-four hour broth culture was therefore made into the mucosa about the pylorus at laparotomy by opening the stomach on the greater curvature and forcing the mucosa of the lesser curvature through it. Many small blebs with the culture were made proximal to the pylorus. It is impossible to raise a superficial bleb in duodenal mucosa as it is extremely friable and rubs off easily. This may have some bearing on the site of ulcer being extremely common in the duodenum, which is easily injured.

A black silk thread which had been left in a twenty-four hour broth culture was passed under the submucosa by means of a longitudinal incision through the muscle layers of the lesser curvature just proximal to the pylorus, and then left in place, the muscle layers being closed over it.

After two months, both of these dogs were reoperated on. The mucosa of the first was normal, not showing any pathologic change. There was only scar tissue present in the second dog, and the alpha streptococcus was not obtained by cultures made from the thread which was lying in the muscle layers with normal underlying mucosa and adjacent stomach wall. Both of these dogs had received injections of culture 23d. As it was believed that artificial cultivation might reduce the virulence of the organism, the first growth obtained of cultures 47b and 53 was injected into the mucosa of the respective dogs described previously. Forty-five days later, at reoperation, the mucosa in both dogs appeared normal in every respect.

It would therefore seem that the intramuscular or submucosal injection of the alpha streptococcus cultivated from human ulcers will not produce an ulcer in the dog in this manner. It is interesting, however, that with intramuscular injection there was considerable thickening and induration after twenty-five days and that the organism was recovered.

All the rabbits that were used in the preparation of the serum and that received repeated small intravenous doses of the living organisms washed in sterile saline solution, at autopsy showed no lesions of the stomach or duodenum. Six rabbits died after losing weight rapidly before their serum had reached a high enough titer to use, but showed no pathologic change except small pneumonitis patches.

This would strongly bring out the possibility that those experimenters who have produced hemorrhagic erosions and small ulcerations of the duodenum by large intravenous doses of various broth cultures of streptococci were doing so by a foreign protein anaphylactic type of reaction, which one may easily produce with peptone.

The ulcers produced by the intracutaneous injection in the dog's skin of the alpha streptococcus obtained from human ulcers as shown in *B* and *C* of figure 5, are proof enough of its pathogenic powers. Although smaller than those produced by the alpha-prime strain, the chronicity was the same. They were clear, punched-out ulcers which involved only dermis.

The largest ulcer, the middle one (fig. 5*A*), was produced by an alpha-prime strain recovered by Dr. John Torrey from ulcerative colitis.

The first injections were made subcutaneously, and by this method a lesion was never produced. Only by intradermal injection did an ulcer result. This demonstrates its specificity for dermis; the specificity for mucous membrane is indicated by the fact that the lesions of the mucous membrane of the mouth were always superficial.

These laboratory animals are not subject to spontaneous gastric ulcers and probably enjoy a normal resistance to the causative organism. One could hardly expect to produce these ulcers by a single injection of such a low grade virulent organism as the alpha streptococcus.

AGGLUTINATION OF PATIENTS' SERUMS WITH PROVED GASTRIC ULCER AGAINST THE ANTIGEN OF THE ALPHA GASTRIC STRAIN

Because of the failure of the intradermal skin sensitivity test to cause any more reaction in a patient suffering from gastric ulcer than in one without gastric ulcer, it was felt that the organism did not create a toxin that might circulate in the blood in sufficient amount to produce general sensitization but only a localized toxin. The material used for the test was a filtrate of broth cultures of the gastric alpha streptococcus prepared by the same method as that used for the scarlet fever toxin and supplied to this department by the Lederle Antitoxin Laboratories. It was therefore decided to see whether serum obtained from patients suffering from proved gastric ulcer would contain specific agglutinins for the alpha streptococcus obtained from gastric ulcer.

The following series of thirty-eight patients with proved gastric ulcer, controlled with serum from thirty patients suffering from other types of streptococcus infection, show the encouraging results obtained.

It is apparent from tables 10 and 11 that the most marked agglutination occurs in the most active ulcers, namely, bleeding and perforated. Less marked agglutination occurs in patients who have been under rigid medical treatment for a varying length of time and also in those

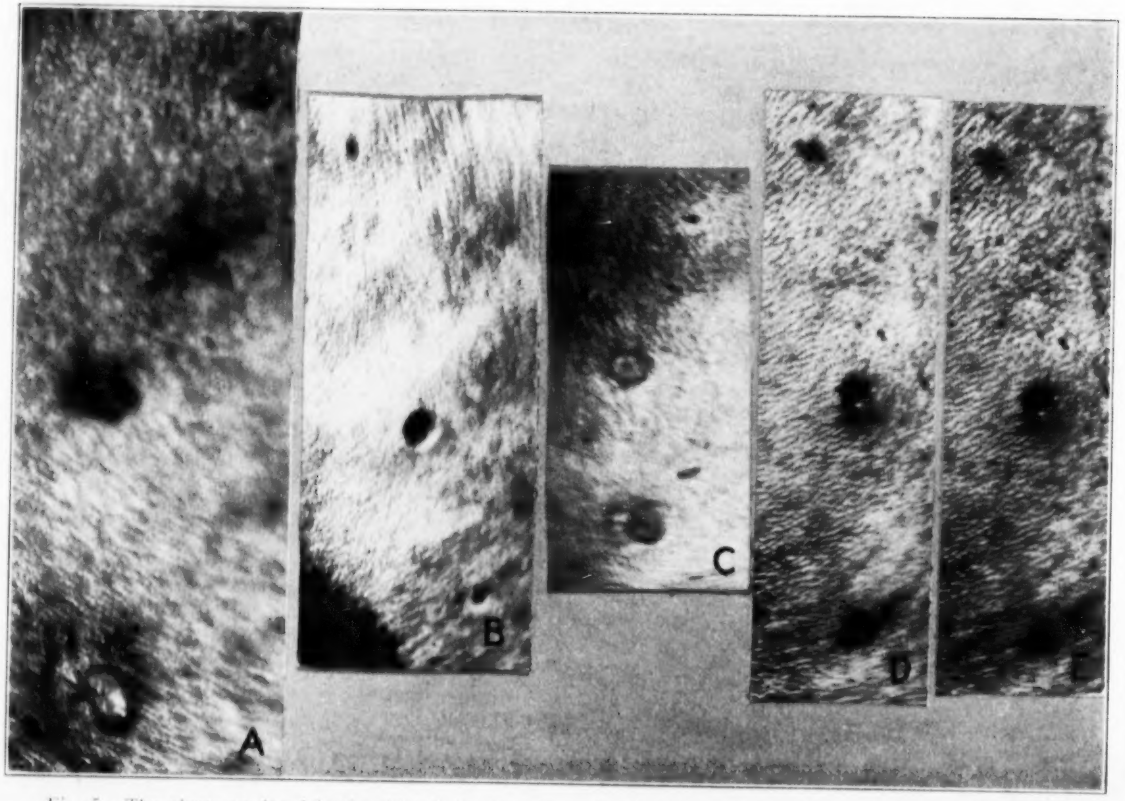

Fig. 5.—The ulcers produced in the skin of the dog shown in the photographs were produced by making injections of 0.5 cc. of a twenty-four hour dextrose broth culture intradermally. *A*, top, alpha-prime strain, culture 5-6; center, ulcerative colitis alpha prime strain, Dr. Torrey; bottom, alpha-prime strain, culture 11. *B*, top, gastric strain, culture 11; center, alpha prime strain, culture 31; bottom, gastric strain, culture 19. *C*, top, gastric strain, culture 23; center, alpha prime strain, culture 29; bottom, alpha prime strain, culture 31. *D*, top, gastric strain, culture 47; *E*, center, alpha prime

in whom pain has recurred without other symptoms for a varying number of years after the ulcer symptoms had been completely relieved. In this type of case, operation usually reveals not an active ulcer but periduodenal adhesions from previous inflammation. It was only in this type that the 1:40 agglutination titer in the ulcer series occurred. None of the serums of the control series went above the 1:40 titer, most of them showing not more than 50 per cent agglutination at 1:20.

A most interesting case is that of R. R. in table 10. This patient had had a gastro-enterostomy six years previously for a duodenal ulcer and had had recurrent symptoms since then. His serum agglutinated to 1:1,280 before operation. A resection was done, and a large gastrojejunal ulcer was found perforating into the colon together with a scarred, practically healed duodenal ulcer. The organism 55 was isolated from the gastrojejunal ulcer, and the scarred healed duodenal ulcer was found sterile. Thirty-six days after resection, his serum agglutinated only to 1:80.

In tables 10 and 11, the highest serum dilution agglutinating the antigen 50 per cent is recorded as the titer. The tests were carried out macroscopically.

COMMENT

The outstanding facts which favor an infectious theory of gastric ulcer are:

1. An alpha streptococcus can be cultivated from practically 100 per cent of active ulcers, in pure culture in a majority of cases.

2. By agglutination and agglutinin absorption, the alpha streptococcus has been proved to be an identical organism. This homogeneity in itself is remarkable because of the proved heterogeneity of the alpha group.

3. The organism has a tendency to form ulcers and attack skin and mucous membrane. It is related but not identical with the alpha-prime strains that are found in ulcers of the skin.

4. The serum of patients suffering from peptic ulcer contains this organism's specific agglutinins, seemingly to a degree proportional with the size, stage and extent of the ulcer. Control serum from non-streptococcal pathologic conditions and serum from patients suffering from other types of streptococcus infection contain much less agglutinins for this organism, generally less than 25 per cent of the amount.

5. Pathologically, the lesion is typical of inflammation elsewhere. The necrotic membrane in the crater of the ulcer is a common manifestation and contains these organisms. Examination of the fresh specimen reveals this condition.

TABLE 10.—*Agglutination of Serum of Patients with Proved Gastric Ulcer with Antigens of Two or Three Gastric Strains* *

Patient	Service†	Ulcer	Symptoms	Duration	Treatment	Gastric Antigen			
						2	23	47b	Strain
P. B.	M4	Perforated duodenal	2 years	2 years	None	1280	1280	1280	
R. R.	M4	Bleeding gastro-jejunal ulcer	Gastro-enterostomy for duodenal ulcer 6 years previously, recurrent symptoms for 6 months			1280	1280	1280	55
J. Y.	L4	Perforated duodenal	10 years	Blood obtained 5 days after simple suture for perforation	None	1280	1280	1280	
L. M.	M4	Gastric	Gastro-enterostomy 6 months previously; symptoms, 5 years			160	320	320	
E. D.	A1	Duodenal gastro-jejunal	Gastro-enterostomy 4 years previously; recurrent symptoms for 3 years		Diet powders	320	320	320	56
P. P.	M4	Perforated duodenal	Simple suture for perforation; symptoms only 5 weeks previously			320	320	320	
G. N.	M6	Perforated pyloric	Simple suture; no induration; no previous symptoms			80	80	80	
J. A.	L6	Perforated duodenal	2 months	Sudden perforation; simple suture		320	320	320	
W. F.	M4	Perforated gastric	3 years	Simple suture; blood 5 days after operation		160	160	160	
D. M.	L6	Duodenal	Perforated and simple suture, 1926; gastro-enterostomy for recurrent symptoms; ulcers present						
H. H.	M3	Pyloric	6 months	Gastro-enterostomy for pyloric ulcer 9 days before		320	320	320	
A. W.	M3	Perforated pyloric	Blood taken thirtieth day after gastro-enterostomy			160	160	160	
H. J.	M5	Bleeding gastric	Severe for 2 years	.....	Not operated on	80	80	80	
H. C.	M6	Duodenal (x-ray)	Severe in spring	10 years	Irregular medical	320	320	320	
J. K.	C.C.	Duodenal (x-ray)	3 years	Recurrent 1 year, pain	Rigid medical, 1 year	160	160	160	
W. K.	L6	Duodenal (x-ray)	5 years	Severe 1 week	Irregular medical	40	40	40	
A. 45507	C.C.	Postpyloric (x-ray)	6 months	Not severe	Rigid medical	160	160	160	
M. W.	1st Surgical	Duodenal (x-ray)	Not severe	6 months	Rigid medical	40	80	40	
I. O.	1st Surgical	Duodenal (x-ray)	Mild	1 year	Rigid medical	160	160	160	
J. C.	1st Surgical	Duodenal (x-ray)	Mild	6 months	Rigid medical	160	160		
C. M.	1st Surgical	Duodenal (x-ray)	Mild	6 months	Rigid medical	160	160		
J. F.	2d Surgical	Duodenal (x-ray)	Pain for 6 months	Known ulcer for 6 years	None previous to rigid medical for 2 weeks	320	320		
A. 45571	C.C.	Postpyloric (x-ray)	Mild	2 years	Irregular medical, then rigid medical for 6 months	80	80		
J. B.	L5	Gastric, perforated	Mild before perforation	2 years	Rigid medical	160	160		
Dr. M.	Private	Duodenal	Healed recurrent	6 years	None	320	320		
H. C.	C.C.	Duodenal (x-ray)	Recurrent pain	2½ years	Irregular medical	160	160		
A. 45813	C.C.	Postpyloric (x-ray)	Pain	2 months	Rigid medical for 2½ years; gastro-enterostomy	80	80		
A. 45471	C.C.	Postpyloric (x-ray)	Mild	1½ years	Rigid medical	80	80		
J. B.	M6	Large old gastric	Severe	10 years	Rigid medical	80	80		
J. N.	M4	Duodenal (x-ray)	Only pain	2 years	Resection of stomach; ulcer size of quarter	160	160		
A. C.	M4	Pyloric (x-ray)	Obstruction	10 years	Rigid medical; free from all other symptoms	80	80		
A. 45433	C.C.	Duodenal (x-ray)	Pain	8 years	Free of symptoms most of time; no treatment	160	160		
A. 46085	C.C.	Pyloric (x-ray)	Pain	3 months	Gastro-enterostomy 6 years previously; recurrent pain	160	160		
L. O.	C.C.	Duodenal (x-ray)	Pain	2 to 3 years	Rigid medical	160	160		
J. J.	L4	Gastric	Pain, indigestion	6 years; recurrent for 3 weeks	No treatment	80	80		
H. J.	L4	Duodenal	Pain	2 years	Resection of stomach; large, size of nickel, lesser curvature	320	320	.....	58
J. C.	1st Surgical	Duodenal (x-ray)	Pain	1 year	Gastro-enterostomy; blood taken 12 days after	80	80		
T. T.	1st Surgical	Duodenal	Typical pain	5 weeks	Rigid medical	160	160		
R. R.	M4		34 days after resection, gastrojejunal ulcer		Rigid medical	80	80		
			Before resection, agglutination 1280			80	80		

* Scales up to 1280 were used in the first three experiments and 1:640 in all the rest; gastric strain 58 was received too late to be incorporated and evaluated in the

6. The rapidity with which an ulcer, no matter how large, will heal following simple suture and not recur for many years or not at all is certainly against any trophic disturbance. Leriche [54] has noted the remarkable results following simple suture when the ulcer was so large

TABLE 11.—*Control Series of Patients with Normal Serum Showing Incidence of Foci of Infection*

Patient	Service	Disease	Focus of Infection	Agglutination 2	23	47b
D. C.	M4	Chronic osteomyelitis	Bone	40	20	20
P. D.	L5	Chronic cholecystitis; duodenitis; cholecystectomy	Gallbladder	40	20	20
A. R.	M5	Chronic cholecystitis; duodenitis; cholecystectomy	Gallbladder	40	40	40
L. P.	M5	Giant cell sarcoma	Bone	20	20	20
M. E.	M5	Ovarian cyst and salpingitis	Fallopian tube	40	40	40
J. G.	M4	Hernia	None	20	20	20
L. M.	M4	Gastric hemorrhage; no ulcer by roentgen examination	Cirrhosis of liver	40	40	40
J. M.	M4	Repeated gastric hemorrhage; multiple transfusions; fatal hemorrhage	Autopsy; large carcinoma of lesser curvature; direct extension through liver	20	20	20
H. H.	M3	Ulcer symptoms; not operated on	X-ray repeatedly negative	40	40	40
A. 45419	C.C.	Ulcer symptoms	X-ray repeatedly negative	40	40	40
A. 45576	C.C.	Ulcer symptoms	X-ray repeatedly negative	40	40	40
A. 45569	C.C.	Ulcer symptoms	X-ray repeatedly negative	20	40	20
C. R.	M4	Cellulitis of arm	Soft parts; streptococcus and staphylococcus	40	40	
J. D.	M4	Hernia	Bad teeth	40	40	
J. G.	M4	Cellulitis of knee	Soft parts; streptococcus and staphylococcus	40	40	
W. M.	M4	Hernia	Bad teeth	40	20	
T. S.	M4	Carcinoma of rectum	Bad teeth	40	40	
S. H.	L4	Hemorrhoids	None	40	40	
M. S.	L4	Hernia	None	20	20	
S. S.	L4	Hernia	None	40	40	
H. P.	L4	Hemorrhoids	Bad teeth	40	40	
H. A.	L4	Compound fracture	None	40	40	
T. M.	L4	Hernia	Bad teeth	40	40	
D. S.	A1*	Acute rheumatic fever; acute endocarditis; acute pain in joints	Teeth, tonsils	40	40	
F. H.	A1	Acute multiple arthritis	Teeth, tonsils	40	40	
T. L.	B1	Multiple infectious arthritis	Teeth, tonsils	40	40	
J. A.	A1	Acute infectious arthritis	Teeth, tonsils	40	40	
M. F.	Ground B	Acute infectious multiple arthritis	Teeth, tonsils	40	40	
R. P.	Ground B	Acute infectious arthritis	Teeth, tonsils	40	40	
M. S.	Ground B	Acute rheumatic fever multiple joints	Teeth, tonsils	40	40	
C. R.	Ground B	Multiple infectious arthritis	Teeth, tonsils	40	40	
V. A.	Ground B	Acute infectious multiple arthritis	Teeth, tonsils	40	40	

* A1, B1, Ground B, from Second Medical Clinic, Cornell.

and so fixed that it could not be resected. If the ulcer were due to a trophic disturbance, such rapid healing could not possibly take place. That acidity is a secondary factor is favored by the fact that the great majority of ulcers occur in the area in which there are alkaline mucous secreting glands. Also, the acidity of the stomach is normal or less than normal in more than 50 per cent of cases of gastric ulcer.

Smithies,[56] in his review of 2,168 cases of peptic ulcers, classified 33.1 per cent as due to infection; 2.6 per cent had no free hydrochloric acid. In 23 per cent, the free hydrochloric acid was below 30, in 41 per cent the free hydrochloric acid values were within the normal range (41 to 50 per cent) and in 33.4 per cent the values were greater than normal.

Acid values, however, probably depend on stasis, the result of spasm or cicatrization, preventing regurgitation of alkaline duodenal contents. Elman[57] has shown the much slower neutralization of an acid test meal in patients with ulcer than in normal patients. Following gastroenterostomy in patients with ulcer, he found that the acid test meal corresponded to that of the normal.

It is probably the spasm, muscle tension and fixation that irritate and prevent healing of the ulcer and not the occasional higher acidity, which is secondary.

Holland[58] found that postpyloric ulcer was five times as common as gastric ulcer and believed that the pars pylorica, the muscular activity of the antrum and valve itself plays an important part, if not in the actual beginning of the disease, at least as a factor which prevents healing.

Anatomically, the duodenum is the region of greatest fixation and the poorest and most tortuous blood supply, as demonstrated by Reeves.[59] The preponderance of ulcer in males may be due to the much greater fixation of the duodenum than in females, as brought out by Wilkie.[60] The good results following resection, therefore, could be due to the fact that it does away with fixation and spasm and leaves a freely movable stomach. Certainly all of the acid secreting glands are not removed by a subtotal resection, for the acid secreting glands extend to the esophagus.

A premise might therefore be made that peptic ulcer is caused by a streptococcus of the alpha type of low grade virulence, which has a tendency to produce ulcers attacking skin or mucous membrane; that it extends and progresses only in the mucous membrane and necrotic surface of the crater; that the underlying layers of the stomach are unable to withstand the continual action of the contents of the stomach as the mucous membrane can and healing is prevented by the resulting

56. Smithies, Frank: Significance of Etiological Factors in the Treatment of Peptic Ulcer, J. A. M. A. **74**:1555 (June 5) 1920.

57. Elman, R.: The Behavior of Gastric Acidity in Duodenal Ulcer and Pyloric Obstruction Before and After Gastroenterostomy, Surg. Gynec. Obst. **49**:34, 1929.

58. Holland: Post Pyloric Ulcer, M. Clin. N. Amer. **8**:232, 1924.

59. Reeves, quoted by Massie: A Synopsis of Views Held by American Authors as to Causation of Gastric Ulcer, Guy's Hosp. Gaz. **35**:374, 1921.

60. Wilkie, D. P. D.: Duodenal Ulcer, Lancet **2**:1228, 1927; Observation on the Pathology and Etiology of Duodenal Ulcer, Edinburgh M. J. **13**:196, 1914.

spasm of a fixed area; that the organism may remain quiescent in the mucous membrane for varying lengths of time depending on the general resistance of the patient, and recurs when other infections are prevalent.

Probably foci of infection play no part, except to aid in lowering the patient's vitality. In reviewing 556 cases, Emery and Monroe[61] recently found that foci of infection were not any more common than with any other group. The great majority of patients at Bellevue Hospital have notoriously bad teeth, but this is not any more prevalent in patients with ulcer than in any other group.

Frick,[62] Wilkie[60] and Coffey[63] concluded from their clinical experience that foci of infection, giving off infected streptococcal emboli with an affinity for gastric and duodenal mucosa, are the initiating cause of ulcer. Coffey goes so far as to state that if foci of infection could be eradicated no patient with ulcer would come to operation.

Jackson, in reviewing many esophageal ulcers, found that local treatment with the aid of the esophagoscope and the eradication of foci of infection usually resulted in the healing of the ulcer.

The evidence here presented showing nonrelationship of the alpha strains from foci in the teeth with the gastric alpha strain rules out this belief.

The spirochetes and fusiform bacilli are by far the most frequent organisms seen in sections of the gum tissue and granulomas at the base of infected teeth, as shown in figure 5 *A*. Streptococci are infrequent. The alpha streptococcus obtained from the base of teeth was not found to be related to the stomach strain serologically.

The most difficult question to answer is, How does this organism get a foothold in the mucosa of the stomach and duodenum? Does the gastritis usually found in practically every case precede or follow? There must be some preceding pathologic change or a localized lowered resistance; otherwise, everyone would be likely to suffer from gastric ulcer. Low grade organisms of this type could not possibly gain a foothold without lowered resistance.

Infants aged from 1 to 6 months, which is the age of incidence of more than 100 reported cases of death due to duodenal ulcer, probably do not have a previous pathologic condition; certainly they have no foci of infection in the teeth, and their only intake is milk. They are all marasmic infants whose resistance to any type of infection is greatly lowered, and the cases seem to occur epidemically. In this way they

61. Emery, E. S., and Monroe, R. T.: Peptic Ulcer: A Study of Five Hundred and Fifty-Six Cases, Arch. Int. Med. **43**:846 (June) 1929.

62. Frick, A.: Medical Treatment of Gastric Ulcer Without Alkalis, J. A. M. A. **82**:595 (Feb. 23) 1924.

63. Coffey, R. C.: Personal Experience in Peptic Ulcer, J. A. M. A. **91**:1 (July 7) 1928.

resemble the occasional outbreaks of severe streptococcic infections of the throat which have been proved to have their source in cow's milk. Jones [64] found hemolytic and faintly hemolytic streptococci commonly in both pasteurized and unpasteurized milk. Because of the organisms' power to resist heat which is practically that of pasteurization, it is possible that this organism might have the same source.

The success claimed by some [65] for foreign protein shock therapy, injections of milk, in the treatment of ulcer could be attributable only to its known effect on micro-organisms.

SUMMARY

The following facts have been established which demonstrate clearly the specificity of the alpha streptococcus obtained from gastric ulcer:

1. The proof obtained by experiment that a nonhemolytic streptococcus of the alpha type, isolated from nine resected gastric, duodenal and gastrojejunal ulcers, was an agglutinogenic and antigenic homolog.

2. Its agglutinogenic and antigenic unlikeness with all alpha strains from foci of infection such as the teeth.

3. Its agglutinogenic and antigenic identity with four alpha strains obtained from four cases of an acute specific disease, characterized by small ulcers of the lip, tongue, buccal membrane and tonsils.

4. Their relation to alpha prime strains producing ulcers of the skin.

5. Their specific agglutination with serums from patients with proved gastric, duodenal or gastrojejunal ulcers controlled against serums from patients with other types of streptococcus infection.

6. The organisms' apparent presence in the lesion in immediately prepared Levaditi tissue sections.

7. The ability to produce ulcer and its relation to an alpha-prime strain definitely producing ulcer. The possibility of their source being cow's milk has been suggested.

If in a large series of cases specific agglutination of the gastric alpha strain continues, which it gives every indication of doing, this department's efforts will be aimed primarily toward determining its source and prevention, and secondarily toward a real vaccine therapy.

16 East Ninetieth Street.

64. Jones, D. G.: Hemolytic Streptococci Found in Milk, J. Infect. Dis. **19**: 236, 1916.

65. Martin, L.: Peptic Ulcer; the Effect of Parenteral Injections of Purified Milk Proteins on the Symptoms and Progress, Arch. Int. Med. **43**:299 (March) 1929.

THE RELATION OF THE DISTRIBUTION AND STRUCTURE OF THE CORONARY ARTERIES TO MYOCARDIAL INFARCTION*

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A description of the usual course of the coronary arteries and of their more common variations is necessary for the present study. As a detailed account of the finer branches of the coronary arteries is of no particular value in understanding the present work, an elaborate description of the vessels will not be presented, and an account of the auricular circulation will be omitted entirely.

THE USUAL DISTRIBUTION AND THE MORE COMMON VARIATIONS OF THE BLOOD VESSELS SUPPLYING THE VENTRICLES

The Typical Course of the Coronary Arteries.—Both coronary arteries arise from the aorta close to its juncture with the ventricle. The right coronary artery originates from the anterior sinus of Valsalva, and passes to the coronary sulcus. It follows along this groove at the juncture of the right auricle and the right ventricle, and gives off branches to the anterior surface of the right ventricle. One or two of these branches extend anteriorly across the conus arteriosus for about half the distance toward the anterior interventricular sulcus, and they usually end in an anastomosis with similar branches from the anterior descending branch of the left coronary artery. The remaining branches generally parallel one another and pass toward, but do not reach, the apex. At the acute or right margin of the right ventricle a fairly large branch, the right marginal artery, leaves the right coronary artery and extends down the acute margin about four fifths of the distance toward the apex. The right coronary artery still proceeds in the coronary sulcus and on the posterior surface of the heart gives off one or more branches which may course toward the apex or may go diagonally toward and end in the posterior part of the interventricular septum. When the right coronary artery reaches the posterior interventricular sulcus, it generally gives off a large branch which travels along the sulcus for about three fifths of the distance from the coronary sulcus

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to the apex, where it generally turns into the interventricular septum. This branch, which may be called the posterior descending artery, gives off many branches to the posterior third of the septum. The right coronary artery generally continues in the coronary sulcus, crossing the posterior interventricular sulcus to reach the posterior surface of the left ventricle. Here it ends by dividing into two or more branches, which extend from the coronary sulcus for about three fifths of the distance toward the apex. These vessels usually do not extend to the left beyond a line from one half to two thirds of the distance from the posterior interventricular sulcus to the obtuse or left margin of the heart. Figure 1 shows the portion of the posterior surface of the heart usually supplied by the right coronary artery.

The left coronary artery arises from the left posterior sinus of Valsalva and almost immediately divides into two main branches. The larger of these branches, the anterior descending artery, proceeds down the anterior interventricular sulcus to the apex, and from this point it generally extends on to the posterior surface of the heart, coursing up the posterior interventricular sulcus usually from a fourth to a third of the distance toward the base of the ventricles. At its termination its branches supply the posterior surface of the apex of both ventricles. As the artery passes down the anterior surface of the heart, it gives off a few small branches which proceed for a short distance to the right to reach the anterior border of the right ventricle. Several large branches leave the anterior descending artery passing diagonally downward and to the left to supply the anterior surface of the left ventricle and the lower portion of the obtuse margin. These arteries have been called the accessory anterior descending arteries by Spalteholz [1] and the rami marginalis by Gross.[2] The anterior descending artery also has many large branches which leave its inferior surface and pass into and supply the anterior two thirds of the interventricular septum.

The other main division of the left coronary artery is known as its circumflex branch. It arises near the origin of the left coronary artery and courses immediately to the left, following the coronary sulcus for a variable distance. It generally passes around the obtuse or left margin of the heart, where it leaves the coronary sulcus to reach and supply the left third or left half of the posterior surface of the basal three fifths of the left ventricle. Some of the rami marginalis (or accessory anterior descending arteries) may take origin from this vessel instead of from the anterior descending artery.

1. Spalteholz, W.: Die Arterien der Herzwand, Liepzig, S. Hirzel, 1924.

2. Gross, Louis: The Blood Supply to the Heart in Its Anatomical and Clinical Aspects, New York, Paul B. Hoeber, 1921.

In the average normal heart, the left coronary artery supplies the entire anterior surface of the left ventricle, the adjacent third of the anterior surface of the right ventricle, the apex of both ventricles, all of the interventricular septum at the apex, the anterior two thirds of the remainder of the septum and the left half of the posterior surface

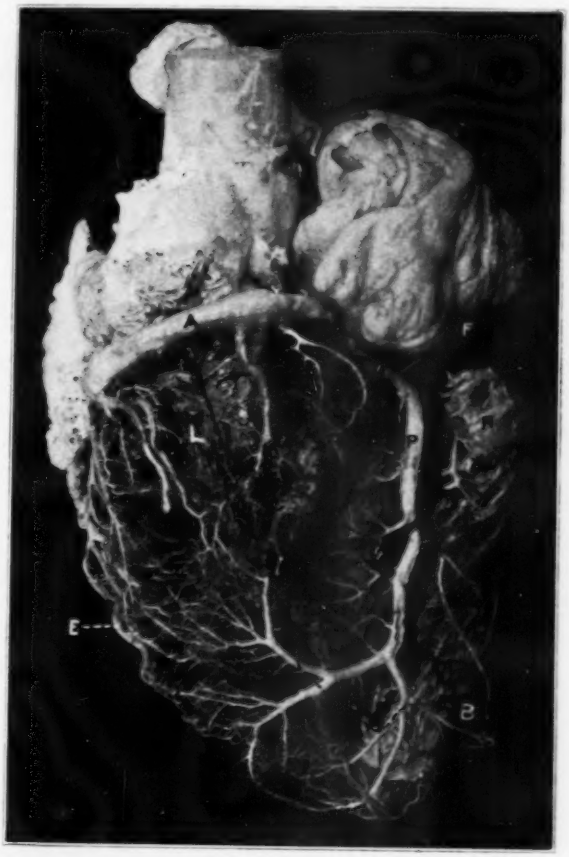

Fig. 1.—Posterior view of heart prepared by celluloid-corrosion method, from a man, aged 42. The vascular preponderance of the left ventricle is evident. *R*, right ventricle; *L*, left ventricle; *E*, left coronary artery; *F*, right coronary artery; *P*, posterior interventricular vein. Broken line from *A* to *B* separates the portions of the heart supplied by the right coronary artery from the portions supplied by the left. This represents almost the average normal line of separation, except in the base of the left ventricle, where the circumflex branch of the left coronary artery supplies a little more of the posterior surface than is usual.

of the left ventricle. It also supplies the anterior papillary muscles and the lower portion of the posterior papillary muscles of the left ventricle as well as most of the anterior papillary muscles of the right ventricle.

The right coronary artery usually supplies two thirds of the anterior surface and all of the posterior surface of the right ventricle, except the apex. In addition, it generally supplies the posterior third of the interventricular septum (except at the apex) and the adjacent half of the basal three fifths of the posterior surface of the left ventricle. The right coronary artery also supplies the posterior papillary muscles, a small portion of the anterior papillary muscles of the right ventricle, and generally the upper portion of the posterior papillary muscles of the left ventricle.

Variations in the Distribution of the Coronary Arteries.—According to Spalteholz, Banchi (1904) found the coronary arteries to have their average normal distribution, approximately as has been described, in 80 per cent of his ninety-two cases. However, there are several definite and comparatively common variations from the average distribution of the coronary arteries. The posterior surface of the left ventricle and the posterior part of the interventricular septum are the regions chiefly affected by these variations.

In four of approximately forty hearts which I have injected, the circumflex branch of the left coronary artery took on unusual significance and resembled the distribution, as usually described, of the corresponding artery in the dog.[3] Banchi found this variation in 10 per cent of the hearts of his series, and Gross in 8 per cent of his. In such hearts, the circumflex artery continues in the coronary sulcus, passes across the entire anterior and posterior surfaces of the left side of the heart to reach the posterior interventricular sulcus, turns down it and courses about three fifths of the distance toward the apex. When the artery passes down the interventricular sulcus, it becomes the posterior descending artery, which is usually a branch of the right coronary artery. The posterior descending artery generally gives off a few small branches to the adjacent portion of the posterior surface of the right ventricle. Thus, not only the whole posterior surface of the left ventricle, but also the entire interventricular septum, and sometimes some of the posterior surface of the right ventricle, as in figure 2, are supplied by the left coronary artery. This is compensated for by the right coronary artery being smaller than usual and generally not supplying any of the septum and perhaps only a portion of the posterior surface of the right ventricle. The distribution of the right coronary artery in the anterior surface of the right ventricle generally is unchanged in the presence of this variation in its distribution elsewhere. Sometimes

3. Whitten, M. B.: A Review of the Technical Methods of Demonstrating the Circulation of the Heart: A Modification of the Celluloid and Corrosion Technic, Arch. Int. Med. **42**:846 (Dec.) 1928. Gross (footnote 2).

both the right and the left coronary arteries supply the basal portion of the posterior part of the interventricular septum.

Spalteholz also published a diagram which was based on Banchi's work and which showed the right coronary artery supplying more of the posterior surface of the left ventricle than in the average heart. Banchi found that the left ventricular branches of the right coronary artery reached to the left almost as far as the obtuse margin in about 17 per cent of the hearts examined, and well around the obtuse margin and on to the anterior surface of the left ventricle in 5 per cent. My series of cases is too small to attempt to establish the frequency with

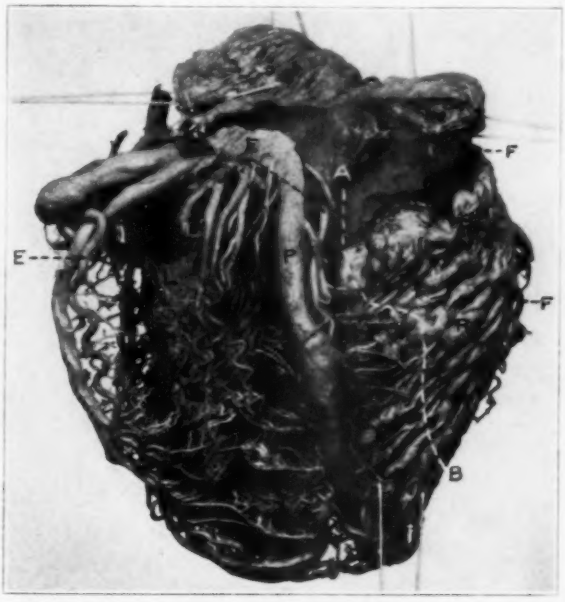

Fig. 2.—Heart, prepared by celluloid-corrosion method, from a woman, aged 55. The left coronary artery supplies the entire posterior surface of the left ventricle and a portion of the posterior surface of the right ventricle. *R*, right ventricle; *L*, left ventricle; *P*, posterior interventricular vein. The broken line from *A* to *B* separates portions of the right ventricle supplied by right and left coronary arteries; *E*, left coronary artery; *F*, right coronary artery.

which this type of distribution of the coronary circulation occurs. However, I have been able to verify the existence of these variations in the amount of the posterior surface of the left ventricle supplied by the right coronary artery (fig. 3).

The extent to which the posterior descending branch of the right coronary artery tends to extend toward the apex of the heart shows a

significant variation in the consideration of infarction. It was stated that, in the average heart, the branches of the right coronary artery extend about three fifths of the distance from the coronary sulcus to the apex, and that the remaining apical portion of the posterior surface of the two ventricles is supplied by the anterior descending branch of the left coronary artery. At times, the posterior descending artery

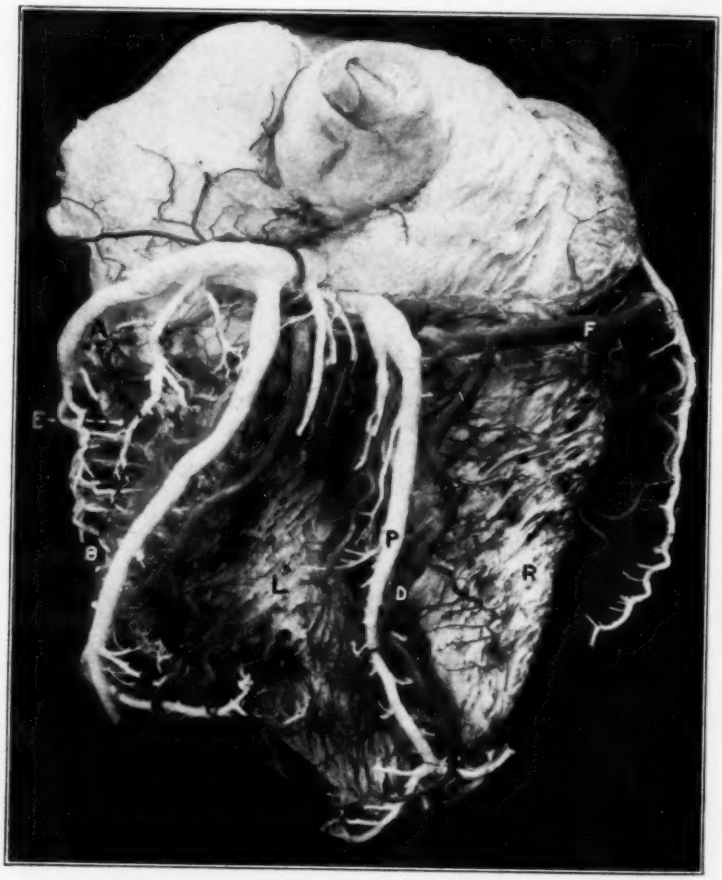

Fig. 3.—Posterior view of heart prepared by celluloid-corrosion method. The right coronary artery supplies the entire posterior surface of the left ventricle and the apex. *R*, right ventricle; *L*, left ventricle; *P*, posterior interventricular vein; *D*, posterior descending artery (right coronary); broken line from *A* to *B* separates parts of left ventricle supplied by right and left coronary arteries; *E*, left coronary artery; *F*, right coronary artery.

extends to and supplies the apex of the heart. This arrangement usually is associated with increased length of the posterior arteries of the left ventricle (right coronary branches) so that they also reach to or nearly to the apex (fig. 3). In the presence of this variation, the apex and almost the entire posterior surface of the left ventricle receive their blood supply from the right coronary artery.

The variations in the coronary arteries which have been mentioned are of the more extreme types. It must be understood that variations which are similar but of lesser degree also exist. In fact, slight variations in the coronary arteries are so common that a heart showing the entire average distribution is rarely encountered.

Fig. 4.—Right marginal artery (artery of the acute margin). This branch of the right coronary artery shows the branching characteristic of the arteries of the right ventricle. The large and small branches lie in the same plane as the artery from which they arise (× 2).

ARCHITECTURAL DIFFERENCES IN THE ARTERIES SUPPLYING THE RIGHT AND LEFT VENTRICLES

Structure of Coronary Arteries.—It has not been emphasized sufficiently that there is a definite difference in the manner of branching of the arteries supplying the right and left ventricles. The deep branches were found by Gross to leave at right angles and to pass straight through the wall of the heart until they reached the subendocardial tissue, where they divided into a mass of fine branches. However, he did not make any distinction between the method of arborization of the vessels of the right and left ventricles.

As a rule, the smaller branches of the right coronary artery supplying the right ventricle spread out over the heart in the same general plane as the subdivisons from which they arise. This type of branch-

ing is illustrated in figure 4. It is characteristic of the normal right ventricle. When the right ventricle is enormously thickened, some of the branches have a tendency to go deep but this is usually under pathologic conditions. An illustration of a heart, in which this condition is present, accompanies another paper.[4] The wall of the left ventricle is much thicker than that of the right in the normal adult heart. The main branches that supply the left ventricle, whether they originate in the right or left coronary artery, course along the surface of the heart just beneath the epicardium (fig. 5 *a*). The vessels leaving these branches do not spread out in the same general plane as the artery from which they arise. Instead, they leave at right

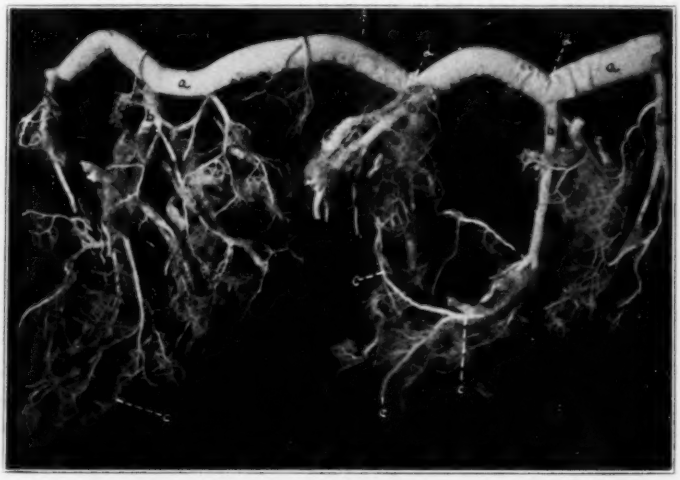

Fig. 5.—Left coronary artery from the left ventricle. *a*, large branch following just beneath the epicardium; *b*, branches leaving at right angles from the inferior surface of *a*, passing directly through the myocardium and having an anchoring effect on *a*; *c*, large and small subendocardial branches; *d*, kinking and constrictions at point at which deep vessels leave to penetrate myocardium (× 6).

angles from the inferior surface of the larger vessel, and penetrate directly through the myocardium (fig. 5 *b*), giving off few branches until they reach the endocardium, where they turn at a sharp angle and end in a mass of fine arterioles (fig. 5 *c*). In figure 5 is illustrated a branch of the left coronary artery from the wall of the left ventricle. It may be seen that the portion of the right coronary artery supplying the left ventricle (fig. 6) has a similar type of branching. When a

4. Whitten, M. B.: A Comparison of the Blood Supply of the Right and Left Ventricles in Childhood, Arch. Int. Med. **45**:46 (Jan.) 1930.

branch of the right coronary artery in the left ventricle (fig. 6) is compared with a branch of the right coronary artery in the right ventricle (fig. 4), a marked difference in the structure of the same vessel in the two ventricles is observed.

Theoretical Consideration.—Branches that leave the surface vessels at right angles to penetrate the myocardium (figs. 5 *b* and 6) and are

Fig. 6.—Branch of right coronary artery from left ventricle. *a*, branch following just beneath the epicardium; *b*, branches leaving at right angles from the inferior surface of *a*, passing directly through the myocardium and having an anchoring effect on *a*; *c*, large and small subendocardial branches; *v*, vein accompanying artery (× 6).

characteristic of the left ventricle appear to immobilize the main arteries. This immobilization, or anchoring, of a main vessel appears to augment its tortuosities, possibly leading to kinking or constriction, with consequent diminution of its lumen at the point of narrowing.

Besides the relative absence of anchorage by deep branches, the right coronary artery, as it swings around the right side of the heart, describes an almost complete semicircle. It is suggested that this, also, is a protection to this part of the right coronary artery; if this vessel becomes sclerosed, it may not become very tortuous because it is free to describe a larger arc. Obviously, however, this mobility is not shared by the portion of the right coronary artery which supplies the left ventricle and the posterior part of the interventricular septum.

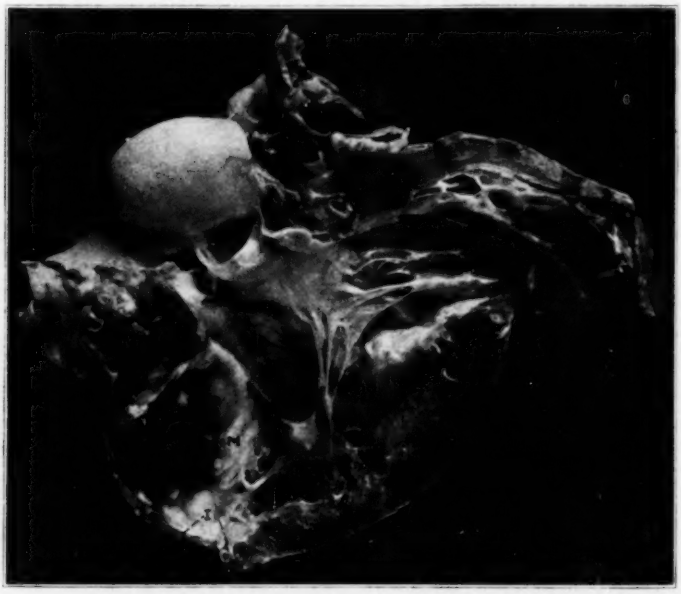

Fig. 7.—Massive infarction of the anterior wall of the left ventricle probably produced by occlusion of one of the larger arteries. There is marked thinning of the ventricular wall. A mural thrombus is present. *M*, mural thrombus; *A*, normal heart muscle above the region of infarction; *I*, old infarct with marked thinning of the ventricular wall.

THE APPARENT RELATIONSHIP OF THE DISTRIBUTION AND STRUCTURE OF THE CORONARY ARTERIES TO MYOCARDIAL INFARCTION

A number of anatomic observations concerning the coronary arteries have been mentioned here. Some of these factors play a part in the production and localization of myocardial infarction.

In a study of infarction in hearts at necropsy, it was noted that three distinct types were present. In some of the hearts a rather large zone

of destruction and fibrosis was found, caused, it was believed, by the occlusion of one of the larger branches of the coronary arteries (fig. 5 *a*). Infarction of this type produced the most extensive lesion found and often was associated with marked thinning of the ventricular wall (fig. 7).

In a number of hearts, a different type of infarction was noted. Those infarctions were recognized generally because of the depression

Fig. 8.—Depression on the posterior surface of the left ventricle due to chronic infarction and resultant contraction of cardiac wall in a localized region. All indentations in the surface of the heart, such as this one, should be incised (fig. 10) at the postmortem examination, or localized infarctions will escape attention. *D*, depression on heart surface.

that they produced on the surface of the ventricle (fig. 8). They were associated with the later fibrous stages of infarction. They were likely to be considered as examples of epicardial thickening and likely not to be recognized at postmortem examination. However, they could be distinguished readily from the "soldier's spots" by the definite indentation they produced in the surface of the heart. If the depressed area was 5 mm. or more in diameter, chronic infarction almost invariably was

found on cutting through the myocardium at that point (fig. 9). This type of infarction seemed to be due to the plugging of one or more of the deep branches (fig. 5 *b*) that leave the surface artery at right angles and penetrate through the myocardium. In this type of lesion the infarction generally extended almost through the myocardium in a zone that corresponded fairly well with the depression on the surface; that is, the chronically infarcted region seemed to have a distribution that roughly paralleled one of the perpendicular branches that penetrated the myocardium. A localized infarction, which passed almost completely through the ventricular wall, was produced. It was believed that the contraction of the resulting scar tissue, in which the longest diameter was perpendicular to the surface of the heart, was responsible for the depressions that were observed in old infarctions of this type.

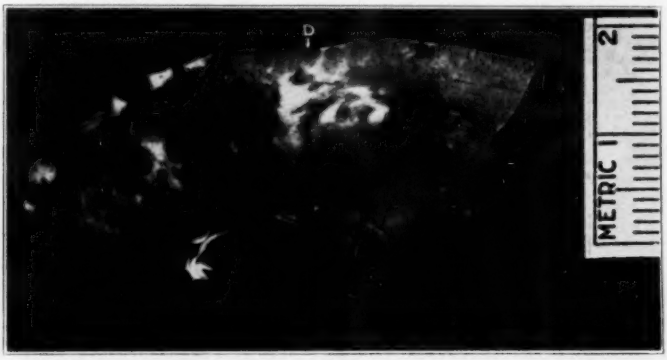

Fig. 9.—A cross-section of the posterior surface of the left ventricle, cut through the depression on the surface of the heart seen in figure 7. The white region of fibrosis deep to the depression is seen; *D*, depression on heart surface.

Karsner[5] may have been referring to this type of infarction when, in describing the pathologic features of infarction, he stated, "The infarct is generally conical in shape with the apex near the epicardium and the base toward the endocardium."

In a third group of hearts the observed infarction was confined to the endocardial third or fourth of the ventricular wall. In infarction of this type (fig. 10), the longest direction of the fibrous zone of replacement was parallel to the endocardium, and the infarction, although it might spread over a considerable area, involved only the subendocardial portions of the wall of the heart. A lesion of this type, although at times it caused some thinning of the ventricular wall, did not produce

5. Karsner, H. T.: Human Pathology, Philadelphia, J. B. Lippincott Company, p. 440, 1926.

indentations of the ventricular surface, as seen in the previous type of infarction, because the fibrotic zone was near to and parallel with the endocardium instead of in a plane perpendicular with the surface of the heart. It was believed that this type of infarction was produced by the occlusion of one or more of the larger subendocardial branches

Fig. 10.—Section through the wall of the left ventricle showing old infarction confined to the subendocardial portion of the cardiac wall and the papillary bundles. *S*, subendocardial infarction; *P*, infarction of the papillary bundles.

(fig. 5 *c*) that course often for a considerable distance in the subendocardial musculature, usually in relation to the columnae carnae or papillary bundles.[6] This is probably the type of infarction observed

6. The part played by the anastomosis or the thebesian veins in the prevention of or recovery from infarction has not been studied in connection with this paper.

by Oppenheimer and Rothschild [7] in their study of arborization block, for they concluded that infarction most frequently was subendocardial.

The frequency with which infarction occurs in the posterior surface of the left ventricle and the infrequency with which it occurs in the right ventricle recently have been emphasized by Parkinson and Bedford. Barnes and Whitten [8] pointed out that in forty-seven cases of myocardial infarction, proved by necropsy, the left ventricle was involved in every case. In thirty-six cases there was infarction in portions of the left ventricle supplied by the left coronary artery, and in twenty-two cases the infarction involved portions of the left ventricle supplied by the right coronary artery. In only four cases was there any appreciable infarction in the right ventricle. In each of these four cases there was involvement also of the posterior surface of the left ventricle which was much more extensive than that occurring in the right, but was confined to the distribution of the right coronary artery.

The structural differences in the arteries supplying the right and the left ventricles are so strikingly at variance that it seems that they may play the major part in the localization of infarction. It has been demonstrated previously that the branches of the arteries of the right ventricle spread practically in the same general plane as that of the artery from which they arise. It has been shown, likewise, that the branches of the arteries of the left ventricle leave the main trunks at right angles and penetrate directly through the myocardium. That these branches leaving at right angles (fig. 5 *b*) have a tendency to immobilize the larger vessels and to cause the tortuosities of the vessels to produce angulation and kinks, with narrowing of the lumen of the main artery, also has been mentioned. This, together with the fact that intimal proliferation and sclerosis of the coronary arteries often is most marked at the points at which these vessels (fig. 5 *b*) leave the main trunks, seems to suggest that the structural differences in the arteries of the two ventricles are closely related to the incidence of infarction in their walls.

It was found that infarction produced in the left ventricle by a lesion of the left coronary artery was much more frequent as a result of disease of the anterior descending artery than of the circumflex branch. If one were to attempt to explain this on an anatomic basis, some difficulty would be encountered, because both arteries supply the left ventricle. However, the anterior descending artery, throughout its

7. Oppenheimer, B. S., and Rothschild, M. A.: Electrocardiographic Changes Associated with Myocardial Involvement with Special Reference to Prognosis, J. A. M. A. **69**:429 (Aug. 11) 1917.

8. Barnes, A. R., and Whitten, M. B.: A Study of the R-T Interval in Myocardial Infarction, Am. Heart J. **5**:142 (Dec.) 1929.

entire length, has many deep branches leaving it at right angles, for this vessel supplies two thirds of the interventricular septum. On the contrary, the first portion of the circumflex artery follows the coronary sulcus and is really above the ventricle itself. Consequently, this portion of the circumflex artery has few deep branches leaving at right angles from its inferior surface, but instead, has a number of large surface branches extending in the direction of the apex. The main branches of the circumflex artery, however, and the circumflex artery itself, as soon as it leaves the coronary sulcus, give off many deep branches which leave at right angles to penetrate the myocardium. It is possible, then, that the circumflex artery is spared somewhat because its first, or supraventricular, portion is not anchored as securely by deep branches as is the entire anterior descending artery.

Infarction caused by occlusion of the anterior descending artery or its branches was most commonly found to involve the apex and the lower half of the anterior surface of the left ventricle as well as a portion of the anterior part of the interventricular septum. The papillary bundles of the left ventricle sometimes were involved. The right ventricle, where it was supplied by the left coronary artery, was generally spared. The infarction produced by occlusion of the circumflex artery or its branches usually involved the obtuse margin of the left ventricle about half way from base to apex, but infarction from a lesion of this artery might also be found at the base and occasionally quite near to the apex. In one heart, infarction of the posterior surface of the left ventricle was produced by occlusion of the circumflex artery. In this heart the circumflex artery was similar to that illustrated in figure 2, and it supplied the posterior surface of the left ventricle and the posterior part of the interventricular septum.

Infarction in the posterior surface of the left ventricle, in the distribution of the right coronary artery, is much more common than has been supposed. There are a number of reasons why infarction in this region has been overlooked so frequently. In the first place, it has been believed for some time that the anterior descending branch of the left coronary artery is the vessel usually involved. In fact, this artery has been named by some "the artery of coronary occlusion" and "the artery of sudden death." No one has ever emphasized the fact that the right coronary artery, where it supplies the left ventricle, has a different type of branching from that which it has in the right ventricle, and is therefore especially vulnerable. Furthermore, the frequency with which occlusion, with resulting infarction, occurs in more than one coronary artery also has escaped attention. Consequently, when infarction has been found in the anterior surface of the left ventricle, often careful search has not been made for infarction in the distribution of the right coronary

artery. Also, infarction at the apex generally has been assumed to have been produced by a lesion in the anterior descending artery, and it has not been recognized that infarction in this situation may be produced by occlusion of the right coronary artery when that vessel, as occasionally happens, extends to the posterior surface of the apex. Many infarctions in the posterior surface of the left ventricle are overlooked if the examination of the heart does not include an incision through the posterior surface of the left ventricle. Recent infarction may not be recognized grossly, and may be overlooked microscopically if sections are not taken from the regions most frequently infarcted. Also the importance of an examination of all indentations of the surface of the heart, such as the one illustrated in figure 8, has not been sufficiently emphasized. If these depressions are 5 mm. or more in diameter they should be cut into as they often represent the contracted scar of an old infarct. Finally, it has not been known that infarction of the posterior surface of the left ventricle produces electrocardiographic changes distinctly different from those of infarction of the anterior surface of the left ventricle.

When infarction occurred in the region supplied by the right coronary artery it was situated almost always in the posterior part of the left ventricle. The site of this infarct naturally varied somewhat with the extent to which the posterior surface of the left ventricle was supplied by the right coronary artery. The infarct often was found to lie near the termination of the left ventricular branches of the right coronary artery. If the right coronary artery extended to the obtuse margin, or to the apex, a portion of the infarction might occur in the region usually supplied by the circumflex or by the anterior descending branch of the left coronary artery. The infarct more frequently involved the posterior wall of the left ventricle than the interventricular septum. Just why the posterior descending artery should be less frequently involved than the left ventricular branches of the right coronary artery is difficult to explain.

It was suggested that occlusion occurred as frequently as it does in the portion of the right coronary artery that supplies the left ventricle because in the left ventricle the right coronary artery takes on a type of branching that differs definitely from that which it possesses in the right ventricle. Furthermore, in the left ventricle, the branches of the right coronary artery are similar to the branches of the left coronary artery which supply the left ventricle, and probably are equally liable to occlusion.

Grossly recognizable infarction was not found in the right ventricle except in four of forty-seven cases of myocardial infarction. In each of the four hearts, there was much more infarction in the adjacent portions of the left ventricle and interventricular septum, whereas the infarction

of the right ventricle was in the portion adjacent to the septum, and was minimal in amount. Infarction in the right ventricle, because of its association with extensive infarction in the adjacent portion of the left ventricle, usually was found in the presence of an occlusion of a large branch of the right coronary artery. The vessel most commonly involved was the posterior descending artery, which supplies the posterior portion of the interventricular septum and a portion of the adjoining right and left ventricles.

Evidence of infarction was not found on the anterior surface of the right ventricle in association with occlusion of the anterior descending artery, even though the septum was extensively involved. The small branches which extend to the anterior surface of the right ventricle, from the anterior descending branch of the left coronary artery, evidently receive sufficient anastomosis from the anterior arteries of the right ventricle (right coronary artery) to sustain this portion of the myocardium.

The declaration of Gross that with advancing age there is increasing decline and failure of the right side of the heart, and that this probably is due to changes in the right coronary artery, has been mentioned. The present study of the circulation indicates that the portion of the right coronary artery which supplies the left ventricle keeps pace, in its vascular development, with the left coronary artery in successive decades. Furthermore, it has not been possible to demonstrate the impoverishment of the circulation in the right ventricle which was found by Gross. In fact, in a heart in which there was hypertrophy of the right ventricle there was a definite increase in the vascularity of that ventricle. Also, when the incidence of infarction is considered, the blood vessels in the right ventricle are certainly less vulnerable, and hence more efficient, than the circulation in the left ventricle. Therefore, the evidence indicates that, although the right ventricle has fewer blood vessels than the left, it is much more likely to receive an adequate blood supply even with advancing years.

The recent work of Barnes and Whitten indicates that infarction of the posterior surface of the left ventricle in the region usually supplied by the right coronary artery produces electrocardiographic changes which are distinctly different and opposed to those produced by infarction in the anterior surface of the left ventricle in the region supplied by the left coronary artery. It is possible to recognize the portion of the left ventricle infarcted, and on the basis of the average blood supply to the region involved, to predict with a high degree of accuracy the coronary artery involved. On the basis of these observations it was suggested that in its electrical effects on the T wave the posterior surface of the left ventricle acts oppositely to the anterior portion. It is interesting that the line of division between these two opposing regions

corresponds closely with the plane separating the portion of the left ventricle supplied in the average heart by the right coronary artery from the region supplied by the left.

SUMMARY AND CONCLUSIONS

1. The deep branches of the arteries of the left ventricle leave at right angles and pass directly through the myocardium. The branches of the arteries of the right ventricle spread out in practically the same plane as the larger artery from which they arise.

2. Three distinct types of lesions are produced by infarction involving the left ventricle. The nature of the infarction depends on the site of the occlusion.

3. The fact that the injury in infarction is almost always to the left ventricle, whereas the right ventricle rarely is involved, seems to depend on the differences in the anatomic structure of the arteries of the two ventricles.

4. Infarction in the posterior surface of the left ventricle is much more common than has been heretofore recognized. Infarction at the apex may be due occasionally to occlusion of the right coronary artery.

5. It is suggested that the position of the first part of the circumflex branch of the left coronary artery, while it is in the coronary sulcus and above the ventricle, is a factor in making it less liable to occlusion than the anterior descending artery.

6. Infarction in the right ventricle was found only in connection with massive infarction of the left ventricle and usually was minimal in amount.

7. The right ventricle, although it appears to be less vascular than the left, is not believed to be especially predisposed to failure with age. In fact, the left ventricle is found to be the one to fail most frequently from arterial insufficiency.

THE CLINICAL ASPECT OF APUTRID PULMONARY NECROSIS *

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During the past three years I have encountered a condition arising in the course of lobar pneumonia, which at first I was unable to explain. Usually at the time of resolution, a roentgenogram of the chest would show a perfectly definite cavity which had produced no symptoms. Repeated roentgenologic examinations would reveal the fact that these cavities decreased in size, and at the end of about two weeks they would have disappeared.

REVIEW OF THE LITERATURE

I was unable to find any data in the literature which threw light on this subject until I made a search through the literature pertaining to the pathology of pneumonia. From a study of this literature it became apparent that the clinical aspect of the condition, which was subsequently called "aputrid pulmonary necrosis" by Kaufmann,[1] had never been described. In 1907, Rosenthal [2] of Berlin reviewed the literature and reported one case. He stated that beside the ordinary terminations of lobar pneumonia in abscess, gangrene and carnification, there also occasionally arises a form known as sequestration. This sequestration is a necrosis resulting from a thrombosis of the vessels supplying the affected part of the lung. The cause of the anemic infarction is dependent on the inability to form a collateral circulation, and this in turn is due to multiple thrombi, compression of the blood vessels, particularly the capillaries, by the pneumonic exudate, obliteration of the capillaries by the growth of interstitial connective tissue, anthracosis and weakening of the heart, particularly of the right side. The pathologic features of this condition have been mentioned by Kaufmann,[1] Büdinger [3] and Lebert,[4] and individual cases have been reported by Brinckmann,[5]

* Submitted for publication, July 27, 1929.

* From the Medical Service of the Mount Sinai Hospital.

1. Kaufmann: Lehrbuch der speziellen pathologischen Anatomie, Berlin, G. Reimer, 1904, pp. 103, 226 and 238.

2. Rosenthal, Theodor: Ueber den Ausgang der fibrinösen Pneumonie in aputride anämische Nekrose, Berlin, G. Schade, 1907.

3. Büdinger: Ueber Lungensequester, München. med. Wchnschr. **18**:1874, 1904.

4. Lebert: Traité d'anatomie pathologique, Paris, J. B. Baillière & fils, 1857, vol. 1, p. 738; Klinik der Brustkrankheiten, Tübingen, H. Laupp, vol. 1, p. 802.

5. Brinckmann: Ein Fall von Sequestrierung der Lunge nach Pneumonie, Diss., Kiel, 1897.

Henoch [6] and Kühn.[7] Lauche [8] reported two cases, in one of which necrotic sequestrated lung tissue was found attached to the surrounding lung by a stalk containing the thrombosed vessel. Aufrecht [9] reported a case in which a necrotic sequestrum was removed at operation, after having perforated the pleural cavity. One case was also reported by Auguste-Jean Thomas,[10] who gave some review of the literature. The anemic infarction in this case was discovered at autopsy. Cagnetto [11] mentioned the occurrence of anemic necrosis in the course of lobar pneumonia, and stated that this was seen most commonly in the stage of hepatization, and in the region of the margins of the lung, where the blood flow in the capillaries is slower, and where the collateral circulation is established with greater difficulty. Cagnetto [11] agreed that the development of an anemic infarction was favored by the state of hepatization in the lung with its compression of the capillary bed, previous atheromatous conditions in the pulmonary vessels and emphysema. According to this author the anemic infarctions occurred most commonly in elderly people.

The literature therefore revealed the fact that the condition had been described from a pathologic standpoint, that it had never been suspected clinically, and that therefore none of the patients had ever had a roentgenogram taken of the lungs.

REPORT OF CASES

Case 1.—The first patient seen by me who disclosed this condition was a Russian operator, B. D., aged 24, who was admitted to the hospital in March, 1926. There were a few indefinite physical signs posteriorly over the lower lobe of the right lung. The temperature ranged between 100 and 102 F. The roentgenogram taken on March 15 showed a pneumonic infiltration in this area, and within this an oval cavity about 2 inches (5 cm.) in diameter, showing a fluid level. It was thought that this represented an abscess of the lung. The hemoglobin was 96 per cent; the white cell count was 19,600, with 74 per cent polymorphonuclears. Bronchoscopic examination failed to reveal an abscess, and nothing abnormal was found in the bronchi other than a moderate narrowing of the opening of the branch of the middle lobe with a congestion of the main bronchus surrounding this opening. The whole condition remained obscure to me, because clinically there

6. Henoch: Vorlesungen über Kinderkrankheiten, Berlin, A. Hirschwald, 1903, p. 817.

7. Kühn: Ueber den Ausgang der kindlich kroupösen Pneumonie in Lungensequestrirung, Arch. f. Kinderh. **37**:278, 1903.

8. Lauche, in Henke and Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, vol. 3, pt. 1, p. 758.

9. Aufrecht: Die Lungenentzündungen, in Nothnagel: Spezieller Pathologie und Therapie, Vienna, Alfred Hölder, 1890, vol. 15, p. 114.

10. Thomas, Auguste-Jean: Un cas d'infarctus anémique du poumon, Geneva, Lausanne, 1913.

11. Cagnetto, G.: Della necrosi anemica, a focolai, come esito raro della pneumonite crupale, Pathologica **3**:532, 1911; Centralbl. f. allg. Path. u. path. Anat. **23**:840, 1912.

was no evidence of an abscess of the lung, there was no etiologic factor, and on bronchoscopic examination, there was no confirmation that there was an abscess of the lung; however, the roentgenogram definitely showed an abscess to be present. The course of the resolving pneumonia was normal; the temperature came down to under 100 F.; the physical signs remained the same, and neither the cough nor the expectoration was in any way remarkable. The second roentgenogram, taken on March 20, showed a marked decrease in the size of the pneumonic area previously reported in the lower lobe of the right lung, and the cavity was half its previous size. On April 1, examination of the chest showed an almost complete disappearance of the infiltration previously reported in the right lung, and the cavity had also disappeared. On April 15, a roentgenogram showed complete disappearance of the infiltration previously reported, so that here there was a resolving pneumonia in a young woman who presented no unusual clinical phe-

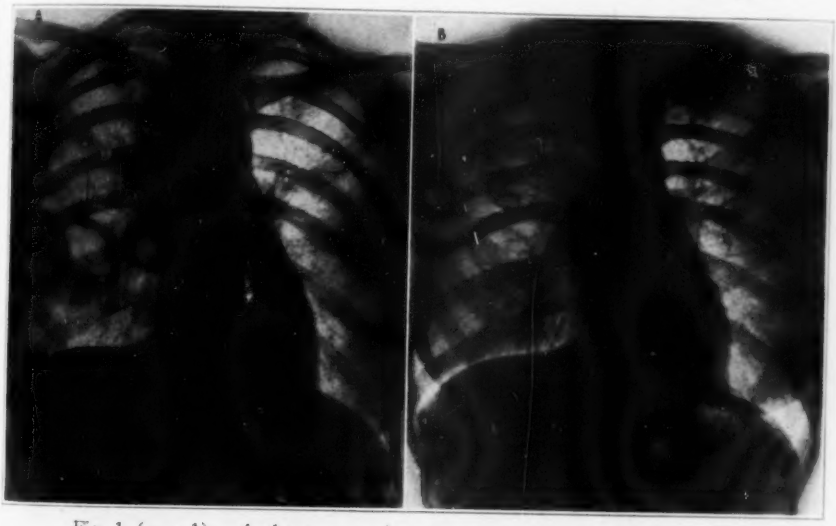

Fig. 1 (case 1).—*A*, the arrow points to a large cavity in the midst of the area of consolidation (March 15, 1926). *B*, complete disappearance of the cavity (April 15).

nomena, and who on roentgenologic examination showed a cavity in the infiltrated area in the lower lobe of the right lung, which in the course of fifteen days cleared up spontaneously. There was no clubbing of the fingers, and the sputum never had a foul odor.

Case 2.—I am reporting the second case through the kindness of Dr. Harry Wessler. A. S., an Austrian housewife, aged 37, was first seen near the end of the pneumonic process, which involved the upper lobe and part of the lower lobe of the left lung. There was a rise in temperature for three weeks after admission to the hospital. The roentgenogram revealed a small abscess in the midst of a resolving pneumonia, the abscess being below the left clavicle. There was no expectoration at any time. On March 10, 1926, the first roentgenologic report showed a pneumonic infiltration involving the upper lobe of the left lung, and at the level of the second interspace a cavity about 2 inches in diameter, showing a

fluid level. On March 17, one week later, examination of the chest showed a marked decrease in the extent and density of the infiltration previously reported in the left lung, and the cavity was distinctly smaller. On March 26, the cavity had completely disappeared.

CASE 3.—D. C., a graduate nurse, who had had a previous attack of pneumonia in 1923, entered the hospital on Jan. 6, 1929, with a history of chill, fever, cough and pain in the chest of twenty-four hours' duration. She had all the signs and symptoms of a right lobar pneumonia, and pneumococcus type III was recovered from the sputum. Blood cultures were negative. The course of the disease was rather severe, ending by crisis on the tenth day, after which convalescence was slow but uneventful. On January 19, roentgenologic examination of the chest showed partial consolidation of the lobes on the right side. The roentgen appear-

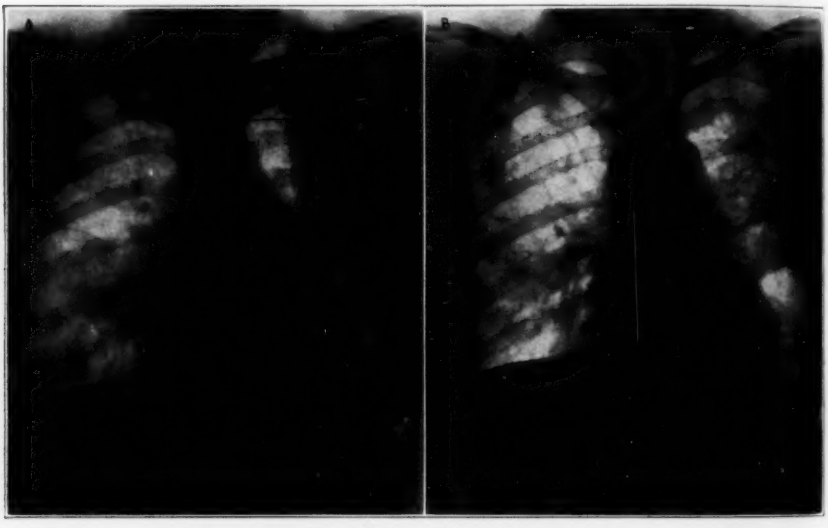

Fig. 2 (case 2).—*A*, the arrow points to the cavity (March 10, 1926). *B*, disappearance of the cavity (March 26).

ance was that of a resolving pneumonic process. The left side was clear. The heart was normal in size and shape. On February 16, examination of the chest showed a faint pneumonic infiltration occupying the right infraclavicular region from the level of the first to the third ribs anteriorly. Within this infiltrated area there was a small cavity, ½ inch (1.27 cm.) in diameter. The patient was again examined roentgenologically on her return from the country on April 2, and examination of the chest showed resorption of the infiltration previously reported in the upper lobe of the right lung, and the cavity previously noted had entirely disappeared. At no time did she have symptoms referable to the cavity, and there was no cough, expectoration, foul breath or clubbing of the fingers.

CASE 4.—V. E., a Spanish housewife, aged 22, entered the hospital twelve days after the onset of bronchopneumonia, with a history of dyspnea, weakness, chilliness and fever. The physical signs were those of resolving bronchopneumonia.

On admission to the hospital the temperature was 102.8 F.; it came down to normal three days after entrance, and remained there. The white cell count was 12,100, with 77 per cent polymorphonuclears. A roentgenogram of the chest, taken on April 17, 1928, showed a pneumonic infiltration at the base of the left lung, with a cavity within it about 1½ inches (3.77 cm.) in diameter. The roentgen appearance was that of an abscess of the lung. There was no cough, expectoration, foul sputum or a foul odor to the breath. The roentgenogram taken on May 3 showed a marked decrease in the pneumonic infiltration previously noted in the lower lobe of the left lung. The cavity was faintly indicated and was somewhat smaller. Three days later, the patient was discharged, symptom-free and having gained 9 pounds (4.1 Kg.).

CASE 5.—M. U., a Polish housewife, aged 40, was admitted to the hospital with a history of severe chill, hemoptysis and pain in the left axilla for two weeks

Fig. 3 (case 3).—*A*, the arrow points to a small area of cavitation in the midst of the area of pneumonic consolidation (Feb. 16, 1929). *B*, the cavity has completely disappeared (April 2).

before admission. The fever lasted for one week, and herpes labialis was present. She remained afebrile for five days, and then two days before admission there was another rise in temperature, and she suffered from a paroxysmal nonproductive cough. Physical examination revealed dulness, diminished breathing and numerous râles at the base of the left lung and left axilla. She was regarded as having resolving pneumonia, but the roentgenogram taken as a routine measure showed the presence of a diffuse infiltration at the lower lobe of the left lung, in the center of which was a cavity with a fluid level. On the basis of these observations, the diagnosis of a postpneumonic abscess of the lung was made. The roentgenologic history of the case was as follows: Jan. 30, 1929: "Examination of the chest showed a collection of fluid at the left base, which showed a horizontal level at the eighth rib posteriorly. This fluid was walled off above. The roentgen examination was more suggestive of a localized collection of fluid and air in the

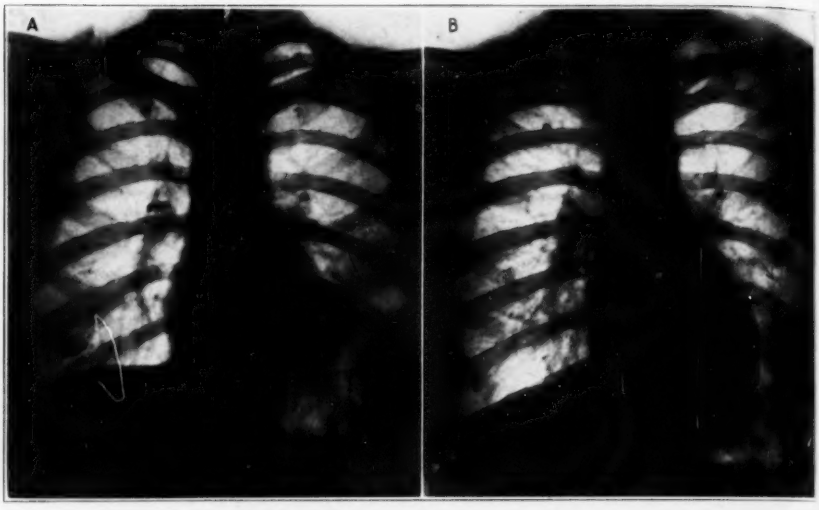

Fig. 4 (case 4).—*A*, the arrow points to a cavity in lower lobe of the left lung (April 17, 1928). *B*, diminution in the size of the cavity (May 3).

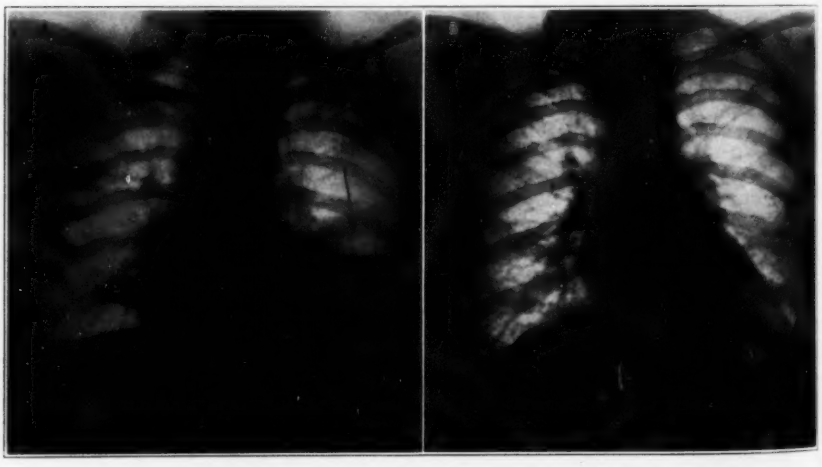

Fig. 5 (case 5).—*A*, the arrow points to a cavity, showing fluid level (Jan. 30, 1929). *B*, the cavity has disappeared (March 1).

pleura than of an abscess of the lung. However, a definite differential diagnosis could not be made." February 5: "Examination of the chest, in comparison with the films of January 30, showed a fairly marked diminution of the consolidation in the region of the left lower lobe. The cavity, however, was still visualized. It showed a fluid level and measured about 1½ inches in diameter." February 11: "Roentgen examination of the chest showed a further decrease in the size of the cavity previously noted in the left lower lobe. From the roentgen and clinical examinations, it was suggested that this might be a case of simple necrosis of the lung following pneumonia." February 20: "Examination of the chest showed a further decrease in the infiltration in the left lung. The cavity which was previously noted had almost disappeared." March 1: "Examination of the chest

Fig. 6 (case 8).—Roentgenogram, showing area of pneumonia (March 19, 1929). No cavity is visible. No subsequent plates were taken. The area of necrosis was discovered at autopsy.

showed a decrease in the area of infiltration previously reported in the left lung. The cavity had completely disappeared." May 15 (follow-up): "Examination of the chest showed almost complete disappearance of the infiltrations previously reported in the left lower lobe. The cavity was no longer seen." The patient did extremely well clinically, remaining afebrile, gaining weight and having little or no cough. Again there was no foul sputum, clubbing of the fingers or profuse expectoration.

Three patients have been seen by me in whom there was no clinical evidence of an area of pulmonary necrosis, nor was roentgenologic evidence obtained, mainly because the patients were too ill to have

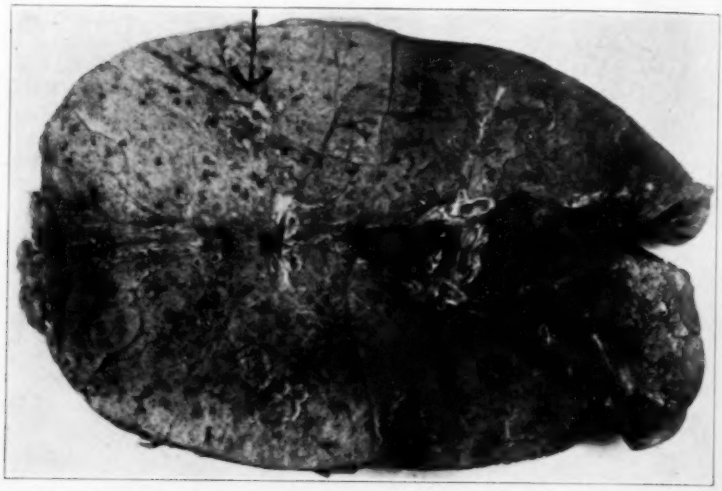

Fig. 7 (case 8).—Gross section. The arrow points to the area of aputrid necrosis.

Fig. 8 (case 8).—Gross section. The arrow points to the area of aputrid necrosis.

repeated roentgenograms taken. These patients (cases 6, 7 and 8) died and came to autopsy.

CASE 6.—I. S., a Greek peddler, aged 38, entered the hospital five days after the onset of illness, showing signs of pneumonia of the upper and middle lobes of the right lung. The course of the disease was severe and the patient died on the eighth day after admission. Autopsy disclosed a lobar pneumonia of the upper and middle lobes of the right lung. The lung appeared grayish red and granular and contained a number of small loculated cavities containing yellowish material. Microscopic examination showed thrombosis of the arteries to the region of a caseating cavity.

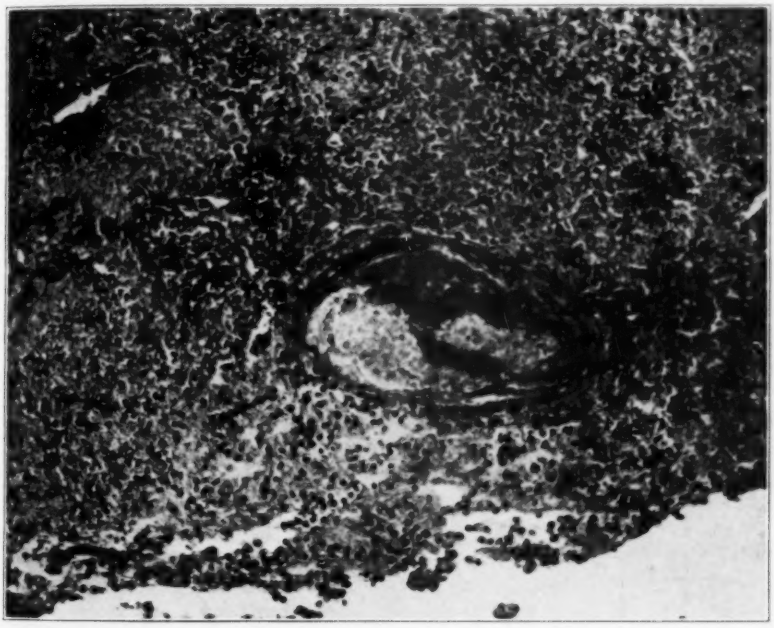

Fig 9 (case 8).—Thrombosed artery outside the wall (infiltrations).

CASE 7.—M. W., a Russian, aged 64, entered the hospital desperately ill with pneumonia of the upper lobe of the left lung and myocardial insufficiency; he died within thirty-six hours of admission. Postmortem smear and culture of the lung showed pneumococcus type II. The upper lobe of the left lung was in gray hepatization. In the lower part of the lobe, there was a sharply delimited area of necrotic lung tissue that had no foul odor. The area measured about 5 cm. in diameter.

CASE 8.—E. K., a Hungarian housewife, aged 34, entered the hospital on March 17, 1929, on the second day of an acute illness, with pain in the right side of the chest and the physical signs of pneumonia of the upper lobe of the right lung. She had a type II pneumococcus in the blood. The white cell count was 22,900,

with 90 per cent polymorphonuclears. The course of the disease was extremely stormy, and in spite of cardiac stimulation and the use of the oxygen tent, the patient died on the ninth day after admission to the hospital. An abstract of the important features of the autopsy was supplied by Dr. Rabin and read as follows: "Lobar pneumonia, right upper and middle lobes in gray hepatization. Lobar pneumonia, right lower lobe, in red hepatization. In the middle of the right upper lobe are two areas of necrotic lung tissue rather sharply demarcated from the surrounding lung. No bronchial communication can be made out. The cavity does not fill on injection of the bronchial tree with NaI. The bronchi show no change and contain no secretion. Microscopic examination shows the involved area to consist of a cavity filled with polynuclear cells. The wall shows necrotic lung tissue, but no increase in infiltration over the surrounding consolidated lung—thus differing from the ordinary abscess cavity. In the wall are a number of thrombosed blood vessels. Outside the cavity there is an artery whose wall is infiltrated, and whose lumen contains a thrombus."

COMMENT

From a study of the cases that I have described clinically and an examination of the roentgenograms, and from the evidence supplied by the autopsy reports, it appears that in the course of lobar pneumonia areas of aputrid necrosis may occur within the infiltrated area. These areas of pulmonary necrosis produce neither symptoms nor signs. There is no clubbing of the fingers or increased cough, and the sputum does not become foul. The condition is not suspected clinically, and is brought to light, if at all, by a roentgenogram of the chest taken as a routine measure. From what I have learned, it would seem that the sequence of events is as follows: Given the conditions that are as conducive to thrombotic phenomena as those present in the stage of hepatization in lobar pneumonia, there probably occurs a thrombosis of a vessel leading to a portion of the involved lung; the occurrence of this thrombosis is favored by any one or more of the following phenomena: (1) the pulmonary compression exercised by the pulmonary exudate, (2) compression of the capillary bed, (3) increased coagulability of the blood during the course of pneumonia, (4) lowering of the blood pressure and (5) myocardial failure with attendant slowing of the circulation. When thrombosis of the vessel has taken place, the portion of the pulmonary tissue supplied by this vessel becomes the site of infarction and subsequent necrosis. This area produces the picture of an abscess cavity in the roentgenograms. I have thought that the disappearance of these areas in so short a time was due to autolysis in the involved zone. The absence of cough and sputum is caused because the area of pulmonary necrosis did not communicate with the bronchus, and I have felt that the noncommunication of this area with the bronchus supplies the reason for the absence of the anaerobic infection, which occurs so commonly in connection with abscess of the lung.

I have searched the literature and have failed to find a clinical description of this condition. If a roentgenogram were taken as a routine procedure in resolving pneumonia, I feel certain that aputrid pulmonary necrosis would be disclosed with much greater frequency, and if searched for at autopsy would probably be found as a rather common occurrence. The areas are easily overlooked in a cut section of the lung at autopsy, and unless one knows that the condition does occur, it is readily missed.

SUMMARY

1. The clinical history and roentgenologic observations of five cases of aputrid pulmonary necrosis have been described.

2. The clinical course and autopsy observations in three others were described.

3. Aputrid pulmonary necrosis produces no symptoms.

4. It is either discovered as a roentgenologic observation or disclosed at autopsy.

5. It is probably not an uncommon observation if looked for.

6. Aputrid pulmonary necrosis is differentiated from abscess of the lung complicating pneumonia by the absence of increased cough, foul sputum and clubbing of the fingers and by the fact that the cavity heals spontaneously in a relatively short time.

THE INFLUENZA EPIDEMIC OF 1928

A STUDY OF ITS BACTERIOLOGY*

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AND
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The conflicting opinions concerning the specific cause of the epidemic of influenza in 1918 make a study of the epidemic of 1928 of added importance. In the recent epidemic, though obviously less severe than that of 1918, the condition resembled closely the milder infections of the previous epidemic. The principal reports of the bacteriologic observations of the 1918 epidemic center around: (1) the influenza bacillus, (2) Bacterium pneumosintes and (3) a specific streptococcus. Mathers, Tunnicliff,[1] Jordan,[2] Rosenow[3] and others described a green-producing streptococcus growing characteristically as large, flat, moist colonies on blood agar plates. It was usually capsulated and lanceolate. It was ordinarily not dissolved by bile and did not ferment inulin. Agglutination and absorption experiments indicated a close immunologic alliance of the majority of the strains. Agglutinins, of low titer, were reported in the serum of patients. Tunnicliff demonstrated the development of specific opsonins during the course of the disease, one of the most important proofs of the relation of this streptococcus to influenza.

EXPERIMENTAL DATA

Cultures from the nasopharynx and sputums in the recent epidemic gave almost uniformly a predominating growth of green-producing streptococci. They appeared in large, moist colonies on blood agar plates. They were frequently mucoid. In two instances in which sputum of typical cases was injected into mice, one mouse died in eighteen hours, and the cultures of the heart's blood gave large mucoid colonies although the original cultures on plates of the sputum were not mucoid. From the heart's blood of the other mouse that died

* Submitted for publication, Aug. 26, 1929.

* From the John McCormick Institute for Infectious Diseases.

1. Tunnicliff, Ruth: Phagocytic Experiments in Influenza, J. A. M. A. **71**: 1733 (Nov. 23) 1918.

2. Jordan, E. O.: J. Infect. Dis. **25**:28, 1919.

3. Rosenow, E. C.: Studies in Influenza and Pneumonia: III. The Occurrence of a Pandemic Strain of Streptococcus During the Pandemic of Influenza, J. A. M. A. **72**:1608 (May 31) 1919.

in forty-eight hours, the colonies were not mucoid and were similar to the growth on the original nasopharynx or sputum plates. This would seem to indicate an increased virulence when mucoid. This mucoid character would frequently be lost after long cultivation on artificial medium. The mucoid appearance might return in subsequent transfers to moist mediums. The loss of mucoid character recalls the type 3 pneumococcus in which artificial cultivation is followed by a change to smaller colonies with little or no tenacious quality.

In almost every instance, gram-negative diplococci were present in a proportion of from 10 to 75 per cent of the typical streptococci. This combination of pebbly gray diplococcus colonies and larger green streptococcus colonies was so constant as to make the gross recognition of plates from patients with influenza extremely easy.

TABLE 1.—*Origin of Strains*

Number of Culture	Main Features of the Disease	Day of Disease Cultured	Comment
1	Fever; chills; prostration; pharyngitis	14	Cough only symptom at time of culture
2	Temperature, 101 F.; chill at onset; prostration; pharyngitis	2	
3	Slight rise in temperature, 99.6 F.; prostration	2	
4	Fever; prostration; generalized aching; nasopharyngitis	2	Culture on third day similar in all respets to first culture
5	Fever; prostration; coryza; sore throat; cough; leukopenia	3	
6	Fever; prostration; generalized aching; coryza; cough	2	
7	Fever; generalized aching; headache; weakness; cough	2	
8	Fever; chills; cough; prostration; coryza	5	
9	Fever; chills; generalized aching.....	2	
10	Chills; fever; prostration; cough (lasted four weeks after acute attack)	7	

Microscopically, the streptococci are lanceolate. They were in pairs and short chains. Growth was abundant in dextrose broth, and usually without clumping.

The serum from some of the more typical cases was tested for the presence of agglutinins for this streptococcus. The results were not conclusive. The serums from the patients recovering from the disease contained agglutinins in higher titer than did the control serums. The best results were obtained by the use of one part of serum to three parts of streptococci suspension. Uniform results could hardly be expected. The serum from patients convalescent from pneumonia gives less than 50 per cent positive agglutination results in an equally low dilution. Furthermore, some strains, particularly soon after isolation, are likely to be less agglutinable than others. The convalescent serum from patient 3 agglutinated six of the ten strains. That from patient 6 agglutinated five of ten strains, including the same strains agglutinated by the serum of patient 3.

Virulence tests were made on mice. Sputums 9 and 10 were pathogenic for mice. The flora from cases 1 and 7 and 8 inclusive were not tested for virulence until some time after isolation. Only one strain was virulent at this time. The injection of the filtrate of the broth cultures of virulent strains simultaneously with the suspensions of the avirulent strains did not appear to enhance the virulence of the avirulent streptococci (table 2).

The strains were tested for fermentative ability. The results with nine of the ten strains indicated a close relationship in their common inability to ferment salicin and mannite. All ten strains fermented dextrose, saccharose and maltose. Eight fermented raffinose; eight lactose, and only four inulin. The fermentation of inulin is rather an

TABLE 2.—*Virulence Tests. Attempts to Enhance the Virulence by Simultaneously Injecting Filtrates from Virulent Cultures*

Mouse	Material Injected Intraperitoneally	Result	Postmortem Culture
1	1 cc. filtrate of 8M.....	Chill; recovery	
2	1 cc. filtrate of 9M.....	Chill; death in 15 hours	Heart's blood B. coli Peritoneal fluid B. coli
3	0.5 cc. suspension of 6.....	Death 15 hours	Heart's blood } Streptococcus Peritoneal fluid } recovered
4	0.5 cc. filtrate of 8M; 0.5 cc. suspension of 6	Death 15 hours	Heart's blood } Streptococcus Peritoneal fluid } recovered
5	0.5 cc. suspension of 4.....	Recovery	
6	0.5 cc. filtrate of 8M; 0.5 cc. suspension of 4	Recovery	
7	0.5 cc. suspension of 2.....	Recovery	
8	0.5 cc. filtrate of 9M; 0.5 cc. suspension of 2	Recovery	
9	0.5 cc. suspension of 5.....	Recovery	
10	0.5 cc. filtrate of 9M; 0.5 cc. suspension of 5	Recovery	

inconstant observation in standard, well studied strains of streptococci and even pneumococci. The three strains pathogenic for mice had similar sugar reactions. After passage through mice their sugar fermentations did not change.

Only one of the three atypical strains in the fermentation experiments fermented salicin. One of these (strain 1), was isolated two weeks after the onset of the disease. Although the patient had persistent cough, he had no fever or other symptoms of acute influenza. It is possible that the specific streptococcus had disappeared. This strain fermented inulin. Strains 4, 5, 6, 7, 8 and 9 were typical types and were isolated early in the course of the disease.

The major difference between our fermentations and those of Tunnicliff was the almost complete absence of salicin fementation in our series. Our tests were made after a shorter period of growth on artificial mediums. Possibly her strains acquired this ability on prolonged artificial cultivation (table 3).

Four of the ten strains were dissolved by 10 per cent bile. None of them was dissolved by 5 per cent bile. Fifty per cent bile dissolved all of them. We employed twenty-four hour cultures in dextrose-broth as advised by Kelly and Gussin.[4] All except no. 6 of the bile-soluble cultures fermented inulin. One (no. 2) of the cultures that were insoluble in bile fermented inulin.

Reactions with high dilutions of the toxin in the skin of susceptible persons were not expected. *Streptococcus viridans* and *Pneumococcus* seldom produce toxins giving reactions of 2 cm. in diameter if used in dilutions greater than 1:10. The Berkefeld filtrates of our streptococci grown five days in phosphate broth gave similar skin reactions in dilution of 1:25 in physiologic solution of sodium chloride. They were larger and occurred more frequently in persons known not to have had influenza in the recent epidemic than in the convalescent patients. Possibly those with negative skin reactions were immune as a result of previous abortive or unnoticed attacks of influenza. These are difficult to exclude in such a mild, widespread epidemic.

TABLE 3.—*The Effect of Ox Bile on Broth Suspensions of the Streptococci*

Cultures Dissolved by 10 per Cent Bile	Cultures Insoluble in 10 per Cent Bile
1, 6, $6M_1$, $6M_2$, 8, $8M_1$, 9, $9M_1R$	2, $2M_1$, 4, 5, 7, 10

Some of the persons tested doubtless carried some degree of immunity from previous epidemic or interepidemic infections.

The filtrate of killed cultures was lethal for mice when given in sufficient doses. Intraperitoneal injections were always followed by a severe chill. The mouse would stiffen out, fall on its back and shake violently for from five to ten minutes. As far as our experiments went, there was no proof that the toxin enhanced the virulence of the simultaneously injected streptococci.

A culture (9M) recently isolated from the heart's blood of a mouse was inflated into the nares of guinea-pigs. The guinea-pigs showed no ill effects.

Sputums from acutely ill patients were applied on swabs to the nares of rabbits, with no results. The culture (9M) recently isolated from a mouse was rubbed into the nares of rabbits; there were no symptoms (table 4).

According to Fisher,[5] swabbing the nares of rabbits with 50 per cent phenol so lowered the resistance that otherwise innocuous streptococci were able to produce disease. In the first rabbit, the left nostril was swabbed with phenol. No bacteria were injected. Death occurred in four days. No localized changes were found at autopsy. The changes

4. Kelly, F. B., and Gussin, H.: J. Infect. Dis. **35**:327, 1924.

5. Fisher, quoted by Laughlen: J. Infect. Dis. **44**:33, 1929.

were those of septicemia. An unidentified staphylococcus was isolated. No streptococci were recovered from the heart's blood.

After swabbing the nares of the next rabbit with 50 per cent phenol, we allowed 2 cc. of streptococcus 9M to flow slowly into the nose. The rabbit died in six days. Autopsy showed pneumonia of the lower lobe of the right lung. The streptococcus was recovered from the heart's blood and from the lung. This strain was then called 9MR.

This strain, more virulent for rabbits, was injected into the nares of other rabbits without preliminary preparation. It regularly produced fatal pneumonia, usually limited to the lower lobe of the right lung.

TABLE 4.—*Attempts to Produce Influenza in Rabbits*

Number of Rabbits Used	Basal Culture Before Inoculation	Material Inoculated	Treatment Before Inoculation	Symptoms After Inoculation	Basal Culture After Inoculation	Termination	Observations at Autopsy	Postmortem Culture
2	No streptococci	Swabs with 24 hour broth suspension; 9M	None	None	No streptococci	No ill effects		
2	No streptococci	Sputum from "flu" cases	None	None	No streptococci	No ill effects		
1	No streptococci	No culture	Phenol, 50% in left nostril	Moderate purulent discharge	No streptococci	Death 4 days after phenol	No local changes; septicemia	No streptococci recovered
2	No streptococci	2 cc. broth culture, 9M	Nostril swabbed; phenol 50%	Purulent discharge; sneezing	No streptococci	Death 6 days after phenol	Pneumonia of right lower lobe	Original streptococci recovered from lung and heart's blood
1	No streptococci	9MR	Without phenol	Purulent discharge; sneezing	No streptococci	Death 6 days after phenol	Pneumonia of right lower lobe	Original streptococci recovered from lung and heart's blood

Previous injection of nonlethal doses of the streptococci or of their filtrates protected mice wholly or partly in two of the three attempts (table 5).

In the first acute flare of the epidemic, we attempted to immunize noninfected persons by vaccines made from the early isolated strains. Fifteen people were given five injections each of plate washings killed with phenol and heat, 10 cc. of a salt solution being used for the growth on each blood-agar plate. The doses were approximately 0.5, 1, 1, 1, and 1cc. The subjects were persons living in close contact with patients acutely ill with influenza. One of them, who had lost much sleep in caring for her son, a patient with influenza, developed a mild acute rhinitis. The others did not develop influenza.

Several patients with acute influenza were given from three to five smaller doses of the plate washings. This procedure seemed to shorten

the course and to ameliorate the symptoms when employed early in the disease. The difficulty of evaluating such results is apparent without a large series and the necessary controls.

With the use of suspensions of these streptococci as antigens, cross-agglutination was attempted (table 6). Intravenous injections of killed dextrose-broth cultures were made into the rabbits in graduated

TABLE 5.—*The Effects of Previous Inoculations on the Susceptibility of Mice*

Material Injected, Feb. 4, 1929	Previous Inoculations	Results	Postmortem Culture	
			Heart's Blood	Peritoneal Fluid
9, 1 cc. of broth culture	.....	Death 1 day	Culture recovered	Culture recovered
9, 1 cc. of broth culture	1/21/29 filtrate 9M, 0.5 cc. culture 2, 0.5 cc. 1/29/29 culture 2, 1.0 cc.	Death 1 day	Culture recovered	Culture recovered
8, 1 cc. of broth culture	.....	Death 3 days	Culture recovered	Culture recovered
8, 1 cc. of broth culture	1/21/29 filtrate 8M, 0.5 cc. culture 4, 0.5 cc. 2/1/29 culture 2, 1.0 cc.	Recovered		
6, 1 cc. of broth culture	.....	Death 4 days	Culture recovered	Culture recovered
6, 1 cc. of broth culture	1/21/29, filtrate 8M, 1.0 cc.	Death 9 days	Atypical colonies original 6 (?)	Sterile

TABLE 6.—*Fermentations of Sugars and the Effect on Litmus Milk of the Streptococci*

Culture by Number	Dextrose	Saccharose	Levulose	Maltose	Salicin	Lactose	Mannite	Raffinose	Inulin	Litmus Milk: Acidified	Litmus Milk: Coagulated
1	+	+	+	+	+	+	0	+	+	+	0
2	+	+	..	+	0	+	0	+	+	+	+
2B	+	+	..	+	0	+	0	+	0	+	+
3	+	+	..	+	0	0	0	0	0	+	0
4	+	+	..	+	0	+	0	0	0	+	0
5	+	+	..	+	0	0	0	0	0	+	+
6	+	+	..	+	0	+	0	+	0	+	+
7	+	+	..	+	0	+	0	0	0	+	+
8	+	+	..	+	0	+	0	+	+	+	+
8M	+	+	..	+	0	+	0	+	+	+	+
9	+	+	+	+	0	0	0	+	+	+	+
9M	+	+	+	+	0	0	0	+	+	+	+
10	+	+	..	+	0	+	0	+	0	+	0
10B	+	+	..	+	0	+	0	+	..	+	..
Pneumococcus	+	+	+	+	0	0	0	+	+	+	+

doses. Finally, injections of large doses of the living broth cultures were made. The rabbits lost weight but were not otherwise ill during the period when injections were made. The rabbits were tested for iso-agglutinins at nine day intervals. After a titer of 1:80 or higher was secured, cross-agglutination was attempted. One of our rabbits died during the immunization. There were no changes in the organs except those of septicemia. The orginal culture was recovered from the heart's blood. Another rabbit developed an ascending paralysis and was killed. The brain and spinal cord showed no gross changes.

A gram-negative diplococcus nonpathogenic for mice or rabbits was recovered.

Numbers 1, 5 and 8 showed the most variations in the cross-agglutinations. The serum from the rabbit immunized to no. 8 agglutinated the homologous streptococci in a dilution of 1:320 but frequently failed to agglutinate the other strains. Strains 4, 7 and 10 were alike by the five antiserums and apparently contained the more generalized agglutinins, but 2, 6 and 9 are closely allied. Strains 5

TABLE 7.—*Cross-Agglutination by Rabbit Antiserums* *

Strains	Serum 2	Serum 6	Serum 8	Serum 9	Serum 10
1	o	e	o	o	e
2	e	e	e	e	e
4	e	e	e	e	e
5	o	e	o	e	e
6	o	e	e	e	e
6M	p	e	e	e	e
6Mz	p	e	..	e	e
7	e	e	e	e	e
8	p	o	p	o	e
8M	o	e	..	e	e
9	p	p	o	e	e
9M	e	p	..	e	e
9MR	o	o	o	o	o
10	e	e	e	e	e
Pneumococcus	o	o	o	o	o
Streptococcus from sinus infection	o	o	o	o	p

* In this table, o indicates no agglutination or not higher than 1:10 dilution; p, agglutination, positive 1:80; negative 1:320; e, agglutination 1:320.

TABLE 8.—*Attempts at Protection with Immune Serum*

Culture	Antiserums	Incubation	Result
6M, 0.5 cc. of plate washings	6, 0.5 cc.	None	Death in 12 hours
6M, 0.5 cc. of plate washings	2, 0.5 cc.	None	Death in 12 hours
6M, 0.5 cc. of plate washings	None	30 minutes	Death in 17 hours
6M, 0.5 cc. of plate washings	2, 0.5 cc.	30 minutes	Death in 12 hours
6M, 0.5 cc. of plate washings	6, 0.5 cc.	30 minutes	Recovery
6, 0.5 cc. of broth culture	None	30 minutes	Recovery
6, 0.5 cc. of broth culture	2, 0.5 cc.	30 minutes	Recovery
6, 0.5 cc. of broth culture	6, 0.5 cc.	30 minutes	Recovery

and 8 would seem to be a subgroup that would require further cross agglutination tests to determine the exact relationship. The less agglutinable strain 1 was not perhaps a true type, and it is significant that it was the only strain taken during convalescence. The pneumococcus tested apparently was not related to any of these strains serologically, nor was there any definite relation to the strain from the sinus infection.

The serum from the immunized rabbits was used in brief protection experiments. The serum from the rabbit immunized to streptococcus no. 6 gave complete protection to the mouse injected with a lethal dose of a homologous culture. The serum from the rabbit immunized to streptococcus no. 2 gave no protection against the culture of no. 6.

The gram-negative diplococci from patients 2 and 6 produced homologous antiserums agglutinating in 1 : 100 dilution. The serum from the rabbit immunized to diplococcus no. 6 failed to agglutinate diplococcus no. 2. The serum from the rabbit immunizd to diplococcus no. 2 would not agglutinate diplococcus no. 6. Both antiserums failed to agglutinate any of the other strains of gram-negative diplococci, even in concentrations of 1:10.

The gram-negative diplococci found in constant association with the streptococci were avirulent for mice and rabbits. They grew abundantly on blood-agar and in broth. The blood of rabbits immunized against these diplococci as antigens failed to agglutinate the other strains of diplococci.

Ferrán [6] isolated a gram-positive coccus from the tissues of patients fatally ill with influenza. These cocci were very virulent. The serum of patients convalescent from influenza agglutinated these cocci. He attributed protective powers to the vaccine made from this coccus.

We have never been able to identify *"Bacterium neumosintes"* in any of our cultures.

We looked particularly for Pfeiffer's bacillus but were able to identify it in only one of our cultures.

COMMENT

As the result of the careful work in the previous epidemic (1918) and the bacteriology of the respiratory secretions of the last epidemic Mather's coccus should be tentatively considered the specific cause of influenza until proof is produced to the contrary. It would seem justifiable to attempt immunization with the filtrates of this streptococcus.

SUMMARY

The flora in the sputums of patients acutely ill with influenza were identical in containing two predominating types of bacteria: green-producing streptococci and gram-negative diplococci.

The streptococci of these patients were pathogenic for animals.

These streptococci produced a toxin. Skin tests with this toxin suggested a means of determining susceptible persons.

Vaccines made from these streptococci seemed to have the power of immunizing against the influenza infection.

The green-producing streptococci for the most part reacted similarly in fermentation tests and bile-solubility tests.

These streptococci showed relationship in cross-agglutination experiments.

6. Ferrán, J.: Siglo méd. **83**:401, 1929.

THE RANGE OF EFFECTIVE IODINE DOSAGE IN EXOPHTHALMIC GOITER

II. THE EFFECT ON BASAL METABOLISM OF THE DAILY ADMINISTRATION OF ONE-HALF DROP OF COMPOUND SOLUTION OF IODINE *

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We have previously shown that during the administration of 1 drop of compound solution of iodine (about 6 mg. of iodine) daily to unselected hospital patients with exophthalmic goiter, there usually occurs as marked a reduction in basal metabolism as during the administration of much larger doses.[1] The effect of administering ½ drop of the compound solution (about 3 mg. of iodine) daily has now been observed in twenty unselected hospital patients with the disease.

METHOD

The method was the same as that used in the hospital patients who received 6 mg. of iodine daily, except that 1 drop of a 50 per cent compound solution of iodine (roughly, 3 mg. of iodine)[2] was administered daily in the metabolism laboratory instead of 1 drop of the undiluted solution.

DATA

The data of the twenty cases are summarized in tables 1 and 2. It may be seen that the average basal metabolic rate shortly after

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* From the Metabolism Laboratory and Thyroid Clinic of the Massachusetts General Hospital.

1. Thompson, W. O.; Brailey, A. G.; Thompson, P. K., and Thorp, E. G.: The Range of Effective Iodine Dosage in Exophthalmic Goiter: I. The Effect on Basal Metabolism of Rest and of the Daily Administration of One Drop of Compound Solution of Iodine, Arch. Int. Med. **45**:261 (Feb.) 1930.

2. Owing to the rough method of measurement, the amount of iodine recorded as being contained in 1 drop of compound solution of iodine is approximate, although it was always measured in the same way, using a dropper of the same size. The iodine was kept in a glass-stoppered bottle. We previously noted that when this solution was kept in a corked bottle, some reaction took place between it and the cork, as a result of which the cork was slowly destroyed and the solution became pale.

TABLE 1.—*Summary of the Consecutive Effects of Rest, the Daily Administration of One-Half Drop of Compound Solution of Iodine and of Much Larger Doses Given Immediately Afterward, in Hospital Patients with Exophthalmic Goiter*

Patient				Admission			Rest					On One-Half Drop Compound Solution of Iodine Daily							On Larger Doses							
	Laboratory Number	Age	Height, Cm.	Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	Average Level of Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	Change in Basal Metabolic Rate, Points	No. of Days Before Resting Level Was Reached	Length of Time Effect Was Observed, Days	Average Level of Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	Change in Basal Metabolic Rate, Points	Length of Time Effect Was Observed, Days	Time the Drop Began, Day	Drop in Basal Metabolic Rate in First 24 Hours, Points	Time Required for Maximum Drop, Days	Average Level of Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	Change in Basal Metabolic Rate, Points	Length of Time Effect Was Observed, Days	Size of Dose in Drops, Daily	Total Change in Basal Metabolic Rate on All Doses, Points	Estimated Weight of Thyroid Gland at Time of Operation, Gm.	
Mrs. J. P.	5767	48	173	+88	120	58.3	+59	80	55.0	−29	1	7	+32	80	52.2	−27	12	5	0	5	+38	89	51.8	+ 6	3	30	−21	84	
Mrs. A. E.	5781	56	156	+42	127	63.7	+49	115	61.9	+ 7	0	10	+21	92	60.8	−28	13	1-2	...	11	+21	90	61.2	0	3	30	−28	35	
Mr. C. G.	5817	43	163	+45	99	61.1	+26	92	61.0	−19	1	4	± 0	76	60.9	−20	12	1-2	...	10	+ 5	74	61.7	+ 5	5	30	−21	..	
Miss E. F.	5883	18	163	+57	141	43.6	+41	100	44.6	−16	2	4	+17	95	44.8	−24	12	1	−8	9-10	+16	92	45.7	− 1	6	30	−25	..	
Mr. A. W.	5850	41	170	+65	110	52.7	+54	105	50.8	−11	4	7	+36	76	48.3	−18	15	7	0	7	+27	83	48.4	− 9	5	30	−27	..	
Mrs. E. W.	5933	32	162	+49	107	53.1	+25	94	52.5	−24	2	5	+ 7	85	52.6	−18	10	5-6	0	5-6	+ 4	86	52.6	− 3	6	30	−21	17	
Mr. P. M.	5944	42	168	+63	102	62.2	+42	87	60.5	−21	2	8	+42	117	61.2	0	11	0	0	0	+40	114	60.7	− 2	3	30	− 2	..	
Mrs. M. B.	5957*	37	155	+90	90	48.9	+41	87	46.9	−49	7	10	+35	79	45.3	− 6	12	0	0	0	+31	83	45.5	− 4	4	30	−10	..	
Miss M. P.	5995	17	163	+35	155	43.1	+35	135	42.8	0	0	4	+14	128	42.8	−21	13	1	−16	2	+22	132	41.5	+ 8	3	30	−13	81	
Miss E. M.	6001	16	152	+50	117	42.6	+41	103	41.3	− 9	2	5	+12	88	41.1	−29	11	1-2	...	5	+19	94	41.6	+ 7	2	30	−22	..	
Mr. L. B.	6054	27	172	+62	90	57.5	+64	101	54.3	+ 2	0	4	+24	81	54.3	−40	8	1	−18	5	+13	79	55.3	−11	6	30	− 51	..	
Miss J. P.	6071	18	165	+66	132	51.3	+26	113	49.6	−40	6	8	+19	110	49.2	− 7	7	0	0	0	+ 9	112	49.7	−10	3	30	− 17	..	
Mr. T. B.	6135	23	181	+52	86	60.7	+25	88	61.3	− 7	0	5	+52	94	59.1	+27	7	0	0	0	+26	81	59.3	−26	7	30	+ 1	154	
Miss B. D.	6160	17	166	+22	102	70.5	+18	93	69.0	− 4	0	6	+19	90	66.3	+ 1	10	0	0	0	+22	103	65.5	+ 3	1	60	+ 4	84	
Mrs. F. R.	6166	21	156	+61	125	60.1	+51	113	58.6	−10	1	6	+29	89	59.2	−22	9	1	−10	6-7	+21	93	60.1	− 8	7	30	−30	..	
Mrs. M. C.	6248	25	164	+71	112	50.2	+53	72	49.0	−18	1	5	+52	70	47.8	− 1	10	0	0	0	+35	71	48.5	−17	6	30	−18	128	
Mrs. M. McN.	6261	36	153	+33	103	54.6	+27	89	54.4	− 6	0	7	+15	82	53.9	−12	10	2	0	3	+11	76	54.1	− 4	3	30	−16	37	
Mr. J. B.	6264	38	162	+48	106	51.5	+47	108	50.6	− 1	0	7	+70	124	49.0	+23	12	0	0	0	+36	104	48.6	−34	7	30	−11	164	
Mr. E. K.	6266	43	176	+43	73	62.9	+29	94	60.9	−14	5	6	+12	62	60.9	−17	10	4-5	0	8-9	+13	64	61.3	+ 1	4	30	−16	56	
Mrs. F. F.	6299	59	158	+54	113	46.3	+50	99	45.1	− 4	0	7	+14	69	45.7	−30	12	3	0	8	+ 9	98	46.4	− 5	5	30	−41	36	
Average	All cases (20); all received large doses			+54			+40			−14	2	6	+26			−14	11				+21			− 5	4.5		−19		
	All in which the basal metabolic rate dropped 10 points or more (13)			+53			+42			−11	1	6	+18			−24	11				+17			− 1	4.5		−25		

* The patient received 20 drops of compound solution of iodine by mistake on the fourth day only of the rest period.

TABLE 2.—*Detailed Presentation of Basal Metabolism Data Summarized in Table 1**

Patient	Laboratory No.	Days Before Starting Iodine											Days After Starting Iodine																				
		11	10	9	8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Mrs. J. P.	5767	....	A	....	+88	+65	+65	....	+65	+61	+57	+60	+47	+46	....	+43	+35	+32	+32	+30	+30	....	+34	+33†	+37	+38	S	+36						
Mrs. A. E.	5781	+42	....	+55	+47	....	+63	+51	....	....	+50	+47	....	+43	+37	+42	+31	+31	+33	....	+26	+26	+23	+20	+22†	+20	....	+22	S					
Mr. C. G.	5817	....	....	....	....	....	A	+45	....	+26	+20	+32	....	+20	....	+12	+12	+13	+9	....	+10	+3	−3	+1†	±0	+10	....	....	+5	S				
Miss E. F.	5833	....	....	....	....	A	....	+57	+45	+35	+49	+38	+30	....	+22	+26	....	+25	+21	+21	....	+17	+16	+18	+13†	+22	+18	....	+15	S	+16			
Mr. A. W.	5850	....	....	A	+65	+60	....	+63	+55	....	+49	+50	+55	....	+44	+51	+47	+48	+38	+43	....	+36	+39	+36	+34	+36	+35†	....	....	+42	+25	+28	S
Mrs. E. W.	5933	....	....	....	....	A	+49	+49	+28	....	+24	+25	....	+33	+26	+20	....	+3	+11	+6	+11	+5†	+7	....	+1	+8	+3	−1	S					
Mr. P. M.	5944	....	A	+63	+51	+39	+34	....	+53	+35	+46	+38	+32	+41	....	+44	+29	+47	+42	+48	+45	....	+48†	+43	+38	+39	S						
Mrs. M. B	5967‡	+90	+72	....	+57	+55	+48	+50	+42	+42	....	+40	+35	+32	+38	+41	+29	....	+37	+32	+38	+34	+27	+39	−†	+32	+29	+34	+28	S			
Miss M. P.	5995	....	....	....	....	....	A	+35	+34	....	+36	+36	+20	+14	+13	+11	....	+13	+11	+15	+14	+14	+22	....	+13†	+19	+23	+25	....	RH				
Miss E. M.	6001	....	....	A	....	....	+50	....	+41	+39	+41	+41	....	+34	+26	+19	+15	+10	+10	....	+8	+15	+17†	+21	+17	....	....	....	S					
Mr. L. B.	6054	....	....	....	....	A	....	+62	....	+65	+66	+62	+44	....	+33	+30	+24	+26	+20	+27	−†	+30	+24	+15	+10	+10	+19	....	....	S				
Miss J. P.	6071	....	....	+66	+37	+42	+47	+38	....	+23	+24	+30	+20	+22	+10	....	+22	+22	+17†	+15	+12	+9	....	....	S								
Mr. T. B.	6135	....	....	....	....	A	+32	+27	....	+20	+25	+27	+33	....	+29	....	+42	+50	+54†	+45	+47	+44	....	+24	+28	S	+27	..					
Miss B. D.	6160	....	....	....	A	+22	....	+16	....	+15	+20	+22	+22	+20	+18	....	+19	+20	....	+19	+23	+19	....	+17†	S	+22							
Mrs. F. R.	6166	....	....	....	A	+61	+53	+45	+53	+58	....	+49	+39	+34	+34	+32	+34	....	+26	+30	+31†	+28	+20	+25	....	+21	+18	S	+23					
Mrs. M. O.	6248	....	....	....	A	....	+71	+60	+62	+62	+53	+53	....	+58	+62	+57	+50	+53	+51	....	....	+54†	+46	+51	+48	+45	....	+35	S					
Mrs. M. McN.	6261	....	....	A	+33	....	+34	+28	....	+22	+29	+29	+29	+23	+19	....	+18	+16	+15	+14	+11	+17	−†	+6	+17	S	+11						
Mr. J. B.	6264	....	A	....	+48	+34	+52	....	+52	+50	+46	+43	+48	+41	....	+41	+42	+47	+52	+45	+49	....	+68	+72†	....	+64	+41	+34	....	+37	S	+36		
Mr. E. K.	6266	....	....	A	....	+43	+41	+45	....	+38	+28	+31	+43	....	+37	....	+18	+18	+18	....	+10	+14†	....	+13	+15	S	+12							
Mrs. F. F.	6299	....	....	A	+54	....	....	+59	+60	+61	+45	+55	+45	....	+39	+31	+27	+23	+19	+12	....	+15	+16	+13†	....	+11	+7	....	S	+9				

* A indicates admission to hospital (nos. 5781, 5967 and 6071 were admitted on the 15th, 12th and 13th days, respectively, before starting iodine); S, subtotal thyroidectomy; RH, right hemithyroidectomy.

† represents the time of starting larger doses (30 drops daily).

‡ This patient received 20 drops of compound solution of iodine by mistake on the 8th day only before the dose of ½ drop daily was started.

admission was plus 54 per cent, that after a period of rest it was plus 40 per cent, that during the administration of ½ drop of compound solution of iodine daily it dropped to plus 26 per cent, and during the administration of larger doses given immediately after the small dose, to plus 21 per cent. Of the twenty cases, thirteen (65 per cent) showed a reduction of 10 or more points in basal metabolism during the administration of ½ drop daily, five showed no change, and two a rise. Seven showed a lower level (8 to 34 points) during the administration of 30 drops daily than during the administration of ½ drop. Four of

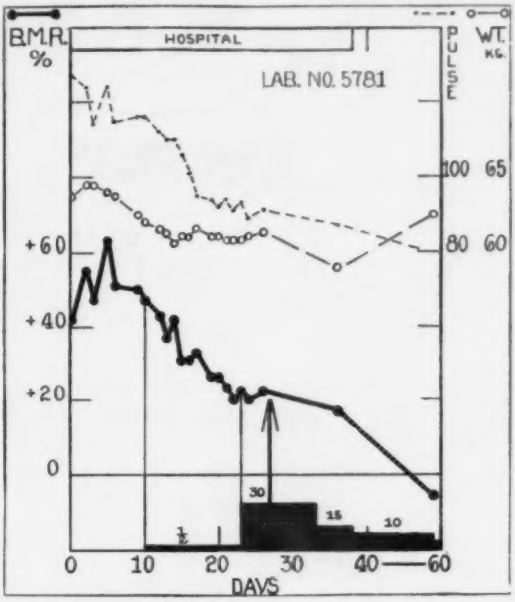

Chart 1.—Well marked reduction in basal metabolism during the daily administration of ½ drop of compound solution of iodine, with no further reduction during the daily administration of 30 drops, preceding a subtotal thyroidectomy for exophthalmic goiter. In this and subsequent charts, arrows denote subtotal thyroidectomies; the black areas represent periods of treatment with compound solution of iodine, and the figures above them, the dosage in drops.

these seven patients were among the seven who showed no reduction during the administration of ½ drop.

Detailed data illustrating various types of response to the doses of iodine employed are recorded in charts 1 to 6.

In chart 7 the effect on basal metabolism of administering ½ drop daily to these twenty patients is contrasted with the effect of administering 1 drop daily to the unselected house patients previously reported.[1]

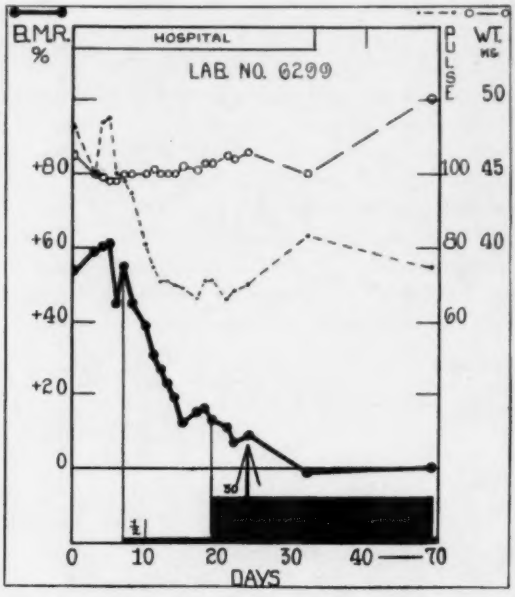

Chart 2.—Well marked reduction in basal metabolism during the daily administration of ½ drop of compound solution of iodine, with no further reduction during the daily administration of 30 drops, preceding a subtotal thyroidectomy for exophthalmic goiter.

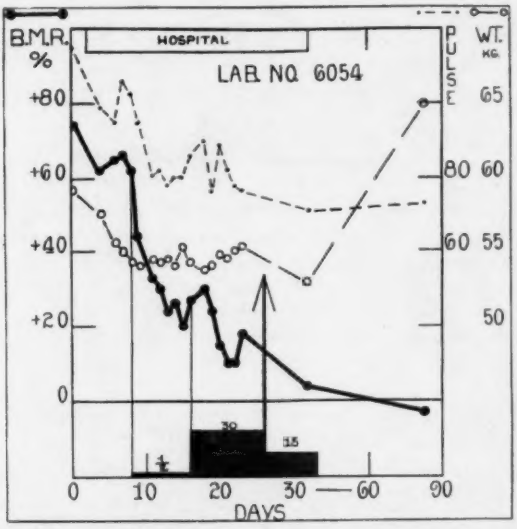

Chart 3.—Well marked reduction in basal metabolism during the daily administration of ½ drop of compound solution of iodine and a further reduction during the daily administration of 30 drops, preceding a subtotal thyroidectomy for exophthalmic goiter.

THE RATE OF DECREASE OF THE BASAL METABOLISM

In the thirteen cases which showed a significant decrease in the basal metabolism during the administration of ½ drop daily, seven days elapsed on the average before the response became maximum. In four cases a reduction of from 8 to 18 points occurred within twenty-four hours. In three cases it was uncertain whether the drop began on the first or on the second day, and in six cases from two to seven days elapsed before any reduction was noted.

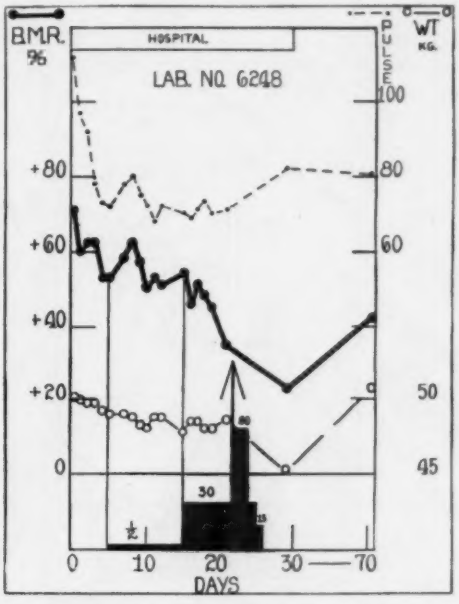

Chart 4.—No reduction in basal metabolism during the daily administration of ½ drop of compound solution of iodine, followed by a moderate reduction in basal metabolism during the daily administration of 30 drops, preceding a subtotal thyroidectomy for exophthalmic goiter.

COMMENT

A comparison of the data with those of the 1 drop series shows two interesting differences:

1. The reduction in basal metabolism on the average was only half as great as in the 1 drop series.

2. The total response of the metabolism to all doses of iodine administered, was less.

Thus, the daily administration of 6 mg. of iodine to hospital patients [1] produced an average reduction in basal metabolism of 27 points (from plus 46 to plus 19 per cent), whereas the daily administration of 3 mg. of iodine produced an average reduction of only 14 points (from plus 40 to plus 26 per cent). This difference is less marked when only cases in each series that actually responded are considered. Thus, fifteen of the seventeen cases in the 1 drop series showed an average decrease of 31 points (from plus 50 to plus 19 per cent), whereas thirteen of the twenty cases in the ½ drop series showed an average drop of 24 points (from plus 42 to plus 18 per cent). This difference, while

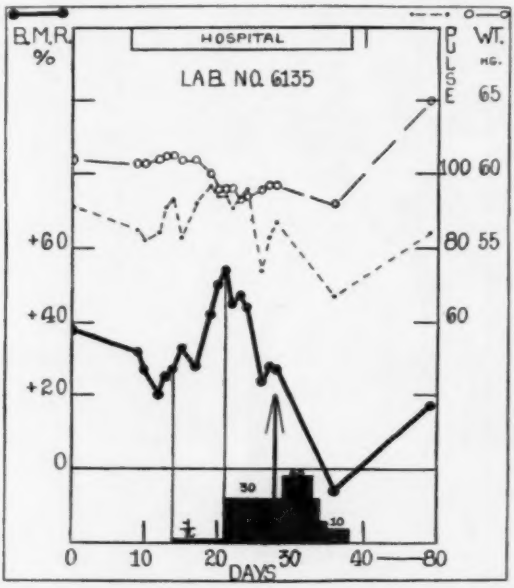

Chart 5.—A rise in basal metabolism and an increase in the severity of exophthalmic goiter during the daily administration of ½ drop of compound solution of iodine, followed by a reduction to the pre-iodine level of basal metabolism during the daily administration of 30 drops, preceding a subtotal thyroidectomy.

in itself not great, appears more important when the results are compared with those in the ¼ drop series.[3] In this connection it is of some interest that whereas the greatest decrease in basal metabolism pro-

3. Thompson, W. O.; Cohen, A. C.; Thompson, P. K.; Thorp, E. G., and Brailey, A. G.: The Range of Effective Iodine Dosage in Exophthalmic Goiter; III. The Effect on Basal Metabolism of the Daily Administration of One-Fourth Drop of Compound Solution of Iodine and Slightly Smaller Doses, with a Summary of Results to Date, Arch. Int. Med., this issue, p. 430.

duced by 1 drop was 49 points, the greatest produced by ½ drop was 40 points.

The difference between the 1 and ½ drop series is apparent from another aspect. Thus, 88 per cent of the cases showed a significant reduction in basal metabolism during the administration of 1 drop of compound solution of iodine daily, and only 65 per cent during the administration of ½ drop daily. Therefore, in most cases of exophthalmic goiter in Boston the difference between 6 mg. and 3 mg. of iodine administered daily determines whether the effect will be marked or moderate.

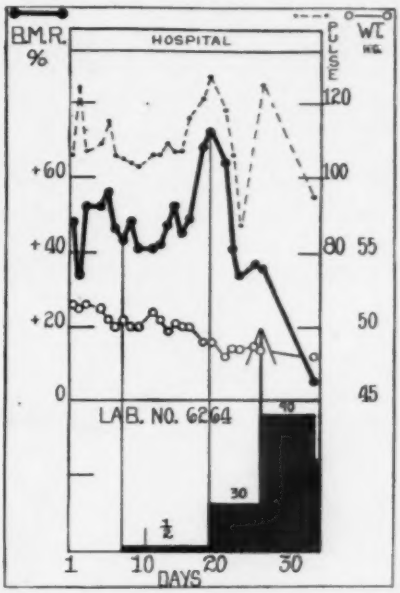

Chart 6.—A rise in the basal metabolism and an increase in the severity of exophthalmic goiter during the preoperative administration of ½ drop of compound solution of iodine a day, followed by a reduction to a level slightly below the pre-iodine level during the administration of 30 drops a day.

Not only was the reduction in basal metabolism during the administration of ½ drop of compound solution of iodine daily less than that during the administration of 1 drop daily, but the total response to all doses of iodine was less in the ½ drop series. Thus, the total drop in basal metabolic rate was 19 points (from plus 40 to plus 21 per cent) on the average in the ½ drop series, and 27 points (from plus 48 to plus 21 per cent) on the average in the 1 drop series (house patients). This difference possibly may be explained by the fact that in the ½ drop

series large doses were administered for an average of only four and one-half days, which is probably an inadequate length of time for them to produce their maximum effect. Thus in the seven cases (5833, 5933, 6054, 6135, 6166, 6248 and 6264) in the ½ drop series in which the effect of large doses was observed for six or seven days, the average basal metabolic rate on admission was plus 54 per cent; after a resting level was established, it was plus 44 per cent; after ½ drop had been given daily for an average of ten days, it was plus 36 per cent; and on 30 drops a day it fell to plus 22 per cent. There is, however, the possibility that the administration of small doses may sometimes interfere with the effect of large doses administered immediately afterward—

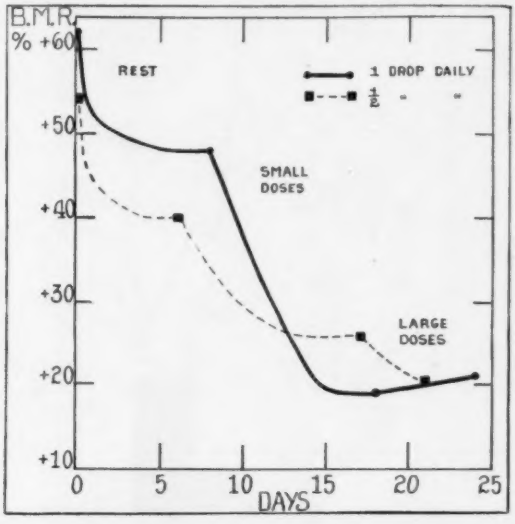

Chart 7.—A comparison of the effect on basal metabolism of the daily administration of 1 drop and ½ drop of compound solution of iodine to two series of hospital patients. In each instance the first point recorded is the average of the basal metabolisms shortly after admission, the second point is the average resting level of metabolism, the third point is the average of the levels to which the metabolism fell during the administration of small doses (½ and 1 drop daily) and the fourth point is the average of the levels during the immediate subsequent administration of larger doses (usually 30 drops daily). In the 1 drop series only those cases are considered in which the effect of larger doses was noted. The points in each series are arbitrarily connected by curved lines, as these denote the actual course of the basal metabolism more nearly than do straight lines.

a conclusion which appears to be upheld by the data on some of the patients in the ¼ drop series. A further comparison of the effects of these two doses will be made in the paper on the effect of administering ¼ drop daily. This paper contains a summary of our results to date.

SUMMARY AND CONCLUSIONS

During the administration of ½ drop of compound solution of iodine (3 mg. of iodine) daily to twenty unselected hospital patients with exophthalmic goiter, thirteen showed a significant reduction in basal metabolism, five showed no change and two showed an increase. Seven showed a lower level of basal metabolism during the subsequent administration of 30 drops daily than during the administration of ½ drop daily.

The average reduction in basal metabolism during the administration of ½ drop of compound solution of iodine daily was 14 points (from plus 40 to plus 26 per cent)—which was only about half as great as that during the administration of 1 drop daily.

The total decrease in metabolism from all doses of iodine was less than in the 1 drop series.

In the thirteen cases that responded, the maximum reduction in basal metabolic rate appeared on the average in seven days. In four cases a reduction occurred within twenty-four hours.

The daily oral administration of 3 mg. of iodine in the form of compound solution of iodine is inadequate to produce a maximum reduction in basal metabolism in most cases of exophthalmic goiter in Boston, whereas 6 mg. is adequate.

THE RANGE OF EFFECTIVE IODINE DOSAGE IN EXOPHTHALMIC GOITER

III. THE EFFECT ON BASAL METABOLISM OF THE DAILY ADMINISTRATION OF ONE-QUARTER DROP OF COMPOUND SOLUTION OF IODINE AND OF SLIGHTLY SMALLER DOSES, WITH A SUMMARY OF RESULTS TO DATE *

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We have already shown that the daily administration of about 6 mg. of iodine in the form of 1 drop of the compound solution produces a maximum reduction in basal metabolism in most hospital patients with exophthalmic goiter,[1] but that the daily administration of about 3 mg. of iodine (½ drop of the compound solution) produces on the average only about half as much reduction.[2] As a continuation of our study of the range of effective iodine dosage in exophthalmic goiter we have now investigated the effect of the daily administration of about 1.5 mg. of iodine (¼ drop of the compound solution) in fifteen unselected hospital patients with the disease. Some observations have also been made on the effect of administering a slightly smaller dose (⅓ drop of the compound solution) to two house patients and to sixteen outpatients. Most of the outpatients had the disease in mild form.

* Submitted for publication, Aug. 26, 1929.

* From the Metabolism Laboratory and Thyroid Clinic of the Massachusetts General Hospital.

1. Thompson, W. O.; Brailey, A. G.; Thompson, P. K., and Thorp, E. G.: The Range of Effective Iodine Dosage in Exophthalmic Goiter: I. The Effect on Basal Metabolism of Rest and of the Daily Administration of One Drop of Compound Solution of Iodine, Arch. Int. Med. **45**:261 (Feb.) 1930.

2. Thompson, W. O.; Thorp, E. G.; Thompson, P. K., and Cohen, A. C.: The Range of Effective Iodine Dosage in Exophthalmic Goiter. II. The Effect on Basal Metabolism of the Daily Administration of One-Half Drop of Compound Solution of Iodine, Arch. Int. Med., this issue, p. 420.

METHOD

The same routine was followed with the ¼ drop series and with the two hospital patients who received ⅕ drop daily, as with the hospital patients who received 1 drop daily,[1] except that 1 drop[3] of a 25 per cent compound solution of iodine (about 1.5 mg. of iodine) and 1 drop of a 20 per cent solution (about 1.2 mg. of iodine) respectively were administered daily in the metabolism laboratory instead of 1 drop of the undiluted solution.

With the outpatients who received ⅕ drop daily, the same routine was followed as with the outpatients who received 1 drop daily.

DATA

The data are summarized in tables 1, 2 and 3.

Seven of fourteen patients (50 per cent) at rest in bed showed a significant reduction in basal metabolism (10 or more points) during the administration of ¼ drop of compound solution of iodine (i. e., 1 drop of 25 per cent solution) daily; six showed no change, and one showed a rise. The average basal metabolic rate shortly after admission was plus 62 per cent; after a period of rest it was plus 43 per cent; after reaching a level on ¼ drop of compound solution of iodine daily, it was plus 34 per cent, and on larger doses administered immediately afterward it was plus 29 per cent. The corresponding figures for the seven cases that responded were plus 63, plus 42, plus 25 and plus 21 per cent, respectively (table 1). The average total drop on all doses for the whole series was only 14 points (from plus 43 to plus 29 per cent), i. e., only slightly more than on ¼ drop.

Data showing various types of response to the administration of ¼ drop daily are recorded in charts 1 to 6.

Except for the two house patients, the data on ⅕ drop are not comparable to those on ¼ drop (1) because the patients were outpatients, and (2) because the majority of them had the disease in mild form.

In one of the two house patients being treated with ⅕ drop daily, a reduction of 14 points in basal metabolism was noted; in the other no change occurred (chart 7). It is of interest that in neither of these was the metabolism any lower during the administration of 30 drops a day than when ⅕ drop was given daily. It is also of interest that all of the outpatients who showed some reduction in basal metabolism with this dose had the disease in mild form, and in only one (no. 5272)

3. Due to the rough method of measurement, the amount of iodine recorded as being contained in 1 drop of compound solution of iodine is approximate, although it was always measured in the same way, using a dropper of the same size. The iodine was kept in a glass-stoppered bottle. We previously noted that when this solution was kept in a corked bottle, some reaction took place between it and the cork, as a result of which the cork was slowly destroyed and the solution became pale.

TABLE 1.—*Summary of the Consecutive Effects of Rest, the Daily Administration of One-Fourth and One-Fifth Drop of Compound Solution of Iodine and of Much Larger Doses Given Immediately Afterward in Hospital Patients with Exophthalmic Goiter*

Patient				Admission			Rest						On ¼ Drop Compound Solution of Iodine Daily								On Larger Doses							
	Laboratory Number	Age	Height, Cm.	Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	Average Level of Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	Change in Basal Metabolic Rate, Points	No. of Days Before Resting Level Was Reached	Length of Time Effect Was Observed, Days	Average Level of Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	Change in Basal Metabolic Rate, Points	Length of Time Effect Was Observed, Days	Time the Drop Began, Day	Drop in Basal Metabolic Rate in First 24 Hours, Points	Time Required for Maximum Drop, Days	Average Level of Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	Change in Basal Metabolic Rate, Points	Length of Time Effect Was Observed, Days	Size of Dose in Drops, Daily	Total Change in Basal Metabolic Rate on All Doses, Points	Estimated Weight of Thyroid Gland at Time of Operation, Gm.
Mrs. M. T.	6344	54	162	+77	123	48.7	+71	110	48.6	— 6	0	4	+64	101	50.9	— 7	11	0	0	0	+61	96	49.3	— 3	7	30	—10	83
Mrs. C. E.	6408	47	157	+42	97	54.9	+27	83	53.7	—15	4	6	+ 1	69	53.6	—26	9	2	0	7	+ 2	72	53.8	+ 1	5	30	—25	24
Mr. R. B.	6413	26	174	+39	72	59.2	+28	79	59.8	—11	1	4	+22	74	59.7	— 6	10	0	0	0	+26	80	59.6	+ 4	4	30	— 2	29
Mrs. E. S.	6423	53	166	+33	108	51.6	+27	108	50.7	— 6	0	12	+23	104	48.9	+ 1	11	0	0	0	+24	108	49.0	— 4	3	30	— 3	25
Mrs. C. D.	6427	41	162	+84	157	44.9	+54	125	42.3	—30	5	7	+30	99	41.8	—24	10	3	—11	3	+28	109	41.8	— 2	4	30	—26	29
Mrs. A. C.	6519	53	157	+73	114	51.4	+51	93	51.3	—22	5	8	+37	85	49.3	—14	8	4	0	4	+20	78	51.2	—17	12	30	—31	34
Miss R. R.	6537	18	149	+52	154	38.7	+30	122	38.1	—22	1	10	+35	126	37.3	+ 5	10	0	0	0	+31	107	38.3	— 4	10	30	+ 1	60
Mrs. A. L.	6539	46	163	+60	99	62.6	+46	83	60.5	—14	2	7	+39	81	57.5	—10	12	1-2	...	1-2	+29	80	56.9	— 7	6	30	—17	154
Mrs. R. S.	6542	41	156	+45	108	71.2	+36	100	70.1	— 9	3	4	+30	69	69.0	— 6	12	0	0	0	+28	71	69.7	— 2	7	30	— 8	43
Mrs. A. B.	6558	20	151	+61	129	50.9	+28	76	46.7	—33	16	18	+15	80	48.7	—13	10	3	0	3	+15	95	50.0	0	3	30	—13	29
Mrs. R. D.	6579	35	154	+53	122	50.4	+47	121	49.3	— 6	0	6	+26	99	48.7	—21	12	3-4	0	8	+31	96	49.0	+ 5	6	30	—16	..
Mrs. M. S.	6586	34	157	+98	140	57.3	+60	115	54.1	—38	4	7	+68	119	52.8	+ 8	10	0	0	0	+44	106	53.5	—24	8	30	—16	120
Miss G. K.	6627	20	163	+87	146	59.8	+59	132	57.3	—28	2	4	+57	116	55.0	— 2	12	0	0	0	+44	112	54.9	—13	10	30	—15	..
Mrs. C. N.	6934	30	169	+67	159	54.2	+41	122	52.7	—26	1	3	+30	109	50.0	—11	17	8	0	8	+24	109	51.1	— 6	8	30	—17	..
Average	All cases (14); all received large doses			+62			+43			—19	3	7	+34			— 9	11				+29			— 5	7		—14	
	All cases in which the basal metabolic rate dropped 10 points or more (7)			+63			+42			—21	5	8	+25			—17	11				+21			— 4	6		—21	
On ⅕ Drop of Compound Solution of Iodine Daily																												
Mrs. V. P.	5193	42	159	+64	102	60.1	+40	84	56.9	—24	6	9	+13	96	54.9	+ 3	9	0	4	4	+43	91	54.5	0	6	30	+ 3	..
Miss A. W.	5203	22	164	+51	98	71.5	+53	96	69.7	+ 2	0	3	+39	91	68.1	—14	9	1	—12	1	+41	89	67.7	....	7	1	—12	200
																					+49	102	67.1	....	2	15		
																					+41	95	65.5	+ 2	11	30		
Average	All cases			+58			+47			—11	3	6	+41			— 6	9				+42			+ 1	13		— 5	
	One case in which the basal metabolic rate dropped 10 points or more			+51			+53			+ 2	0	3	+39			—14	9				+41			+ 2	20		—12	

TABLE 2.—*Detailed Presentation of Basal Metabolism Data Summarized in Table 1*

Patient	Laboratory No.	Days Before Starting Iodine													Days After Starting Iodine*																							
		13	12	11	10	9	8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Mrs. M. T.	6344	....	....	....	....	....	....	A	....	+77	....	+76	+70	+71	+77	....	+72	+57	+65	+56	+68	+69	....	+71	+64†	+71	+64	+67	+67	....	+62	S+59						
Mrs. C. E.	6408	....	....	....	....	....	A	+42	....	....	....	+32	+28	+26	+29	+21	....	+15	+10	+18	−4	+5	+2†	....	+10	−1	+2	S+5										
Mr. R. B.	6413	....	....	....	....	....	....	....	A	+39	+30	+22	+30	+29	....	+28	+27	+27	+24	+24	+22	....	+24	+17†	+24	+28	+27	+25	....	S								
Mrs. E. S.	6423‡	+33	....	+26	....	+40	....	....	....	+28	....	+37	+28	+25	....	+30	....	....	+35	+28	+26	....	+24	+22	+36†	+26	+25	+21	....	S								
Mrs. C. D.	6427	....	....	....	A	....	+84	+75	+68	+65	....	+56	+49	+56	+45	+43	+31	....	+31	+31	+37	+28	+35	+27†	+25	+25	+23	S+37										
Mrs. A. C.	6519	....	....	....	A	+73	+65	....	....	+60	+51	+55	+47	+51	+47	....	+44	+39	+42	+36	....	+39†	....	+30	+23	+27	+27	+25	+22	....	+20	+20	+20	+18	S				
Miss R. R.	6537	....	A	+52	+34	....	+36	....	+31	+35	+20	+44	+31	+25	....	+27	+20	+26	+30	+29	+30	....	+56	+35†	+43	+52	+43	+44	....	+28	+45	+36	+35	+22	RH			
Mrs. A. L.	6539	....	....	....	....	A	+60	....	+47	....	+47	+42	+43	+49	....	+35	....	+36	+35	+37	+31	+38	+37	....	+44	+34†	+31	+35	+38	+52	....	+25	S						
Mrs. R. S.	6542	....	....	....	....	....	....	A	....	+45	....	+45	+35	+36	+44	+37	+38	....	+40	+29	+31	+28	+28	+30	....	+33†	+35	+26	+25	+33	+28	.....	+30	S					
Mrs. A. B.	6558§	Sore throat			....	....	....	....	+38	+38	+34	+27	+26	+30	....	+31	+13	+22	+14	+14	+15	....	+15	+15†	+19	+11	S+26											
Mrs. R. D.	6579	....	....	....	....	....	A	+53	+46	....	+50	+48	+44	+49	+48	+50	....	+42	+32	+36	+33	+27	+27	....	+24	+27†	+30	+33	+31	+33	....	+28	S						
Mrs. M. S.	6586	....	....	....	....	A	+98	....	+70	+75	+61	+61	+62	+58	....	+65	+59	+72	+75	+58	+68	....	+76	+69†	+76	+68	+86	+64	....	+42	+50	RH+39						
Miss G. K.	6627	....	....	....	....	....	....	....	A	+87	....	+58	+55	+63	+62	+63	+58	....	+45	....	....	+64	+59	+54	....	+58†	....	+48	+48	+42	+51	.....	+51	+44	+44	+43	S		
Mrs. C. N.	6634	....	....	....	....	....	....	....	....	A	+67	+46	+40	+42	+39	....	+38	+40	+37	+38	+37	+32	....	+30	+25	+31	+35	+34	+29	....	+31†	+35	+28	+23	+27	+26	..	+23	+228
Mrs. V. P.	5193	....	....	A	+64	....	....	+65	+50	....	+42	+34	+43	+42	....	+39	....	+44	....	+45	....	....	+45†	....	+50	....	+38	....	S+42									
Miss A. W.	5203#	....	....	....	....	....	....	....	A	....	+51	+53	+54	+53	+41	+44	....	+40	....	+40	....	+37	+39†	....	+42	....	+33	....	....	+47†	....	+49†	....	+47	....	+43	..	....	+42

* In the first fourteen cases ¼ drop of compound solution of iodine was given daily; in the last two cases, ⅛ drop. A indicates admission to the hospital; S, subtotal thyroidectomy, and RH, right hemithyroidectomy.

† represents the time when larger doses (usually 30 drops daily) were started.

‡ Admission was on the 15th day before starting iodine.

§ Admission was on the 20th day, and the basal metabolic rates were +61, +53 and +47 on the 19th, 18th and 17th days, respectively, before starting iodine.

The basal metabolic rates were +38 and +43 on the 27th and 29th days, respectively, after starting iodine. The iodine was then omitted.

TABLE 3.—*Summarizing the Effects of the Daily Administration of One-Fifth Drop of Compound Solution of Iodine and of Larger Doses Given Immediately Afterward to Outpatients with Exophthalmic Goiter*

Patient	Laboratory No.	Age	Height, Cm.	Before Treatment: Basal Metabolic Rate, per Cent of Normal	Before Treatment: Pulse Rate	Before Treatment: Weight, Kg.	After Reaching Level on 1/5 Drop of Compound Solution of Iodine Daily: Basal Metabolic Rate, per Cent of Normal	After Reaching Level on 1/5 Drop of Compound Solution of Iodine Daily: Pulse Rate	After Reaching Level on 1/5 Drop of Compound Solution of Iodine Daily: Weight, Kg.	After Reaching Level on 1/5 Drop of Compound Solution of Iodine Daily: Change in Basal Metabolic Rate, Points	After Reaching Level on Larger Doses: Basal Metabolic Rate, per Cent of Normal	After Reaching Level on Larger Doses: Pulse Rate	After Reaching Level on Larger Doses: Weight, Kg.	After Reaching Level on Larger Doses: Change in Basal Metabolic Rate, Points	After Reaching Level on Larger Doses: Size of Dose in Drops Daily	Total Change in Basal Metabolic Rate on All Doses, Points	Comment
Miss L. P.	1709	35	157	+37	95	70.1	+29	96	69.5	— 8	....	...	....	....	..	....	Following subtotal thyroidectomy
Mrs. M. R.	3913	24	159	+18	80	48.3	+ 4	67	49.5	—14	— 3	70	50.3	— 7	15	—21	Following subtotal thyroidectomy
Mrs. E. C.	4675	35	156	+21	98	48.5	+ 7	81	48.7	—14	+ 2	73	47.6	— 5	5	—19	Preceding operation; compound solution of iodine was given previously, but had been omitted for two months
Mrs. E. F.	4906	28	158	+14	80	50.7	+ 4	72	50.0	—10	— 7	64	52.3	—11	1	—21	Compound solution of iodine was given previously, but had been omitted for four months
Mrs. T. P.	4949	56	149	+20	97	53.8	+11	91	54.6	— 9	+ 6	83	51.1	— 5	30	—14	Compound solution of iodine was given previously, but had been omitted for two months
Mrs. M. P. W.	5004	20	166	+23	96	48.5	+16	82	50.6	— 7							Compound solution of iodine was given
				+40	111	48.3	+29	102	49.0	—11	—13	63	55.0	—44	1	—53	previously, but had been omitted for one month
Miss D. B.	5053	24	161	+39	127	46.5	+31	115	47.3	— 8	....	...	....	....	..	....	No other treatment
Miss S. G.	5092	18	148	+23	101	41.9	+33	100	40.3	+10	+28	99	44.9	— 5	15	+ 5	No other treatment
Mrs. E. H.	5168	26	164	+48	108	84.5	+51	107	84.1	+ 3	+37 +28 +29	95 82 80	82.1 81.1 81.3	.... —23	1 5 30	—19	Preceding operation
Miss M. K.	5181	23	163	+46	115	63.7	+38	108	64.3	— 8	+50	115	66.0	+12	1	+ 4	Preceding operation
Miss H. J.	5188	19	154	+33	97	56.3	+21	77	56.0	—12	+14	70	56.1	— 7	1	—19	No other treatment
Miss E. M.	5272	35	166	+47	98	60.9	+26	81	63.6	—21	+18	80	65.5	— 8	15	—29	Following subtotal thyroidectomy
Mrs. V. J.	5306	41	163	+21	107	40.5	+11	76	40.9	—10	+ 2	74	42.3	— 9	5	—19	No other treatment
Miss M. O.	5507	19	155	+37	125	40.7	+31	119	42.9	— 6	+16	108	44.4	—15	5	—21	No other treatment
Mrs. E. C.	5698	52	162	+38	101	57.0	+38	101	56.7	0	+28	95	61.6	—10	1	—10	No other treatment
Average	All observations (16)....			+32			+24			— 8							
	All patients receiving large doses (13).....			+31			+23			— 8	+13			—10		—18	
	All patients in whom the basal metabolic rate dropped 10 points or more; all received large doses (7).....			+28			+15			—13	+ 2			—13		—26	

did the metabolism drop as much as 20 points. In nine of sixteen observations the metabolism did not drop significantly (less than 10 per cent). The average basal metabolic rate before the administration of 1/5 drop daily was plus 32 per cent; after it had had time to produce a maximum effect, it was plus 24 per cent. In thirteen of the sixteen experiments, larger doses were given immediately after the 1/5 drop regimen was finished. In these observations the basal metabolic rate was plus 31 per cent before iodine was given, plus 23 per cent after

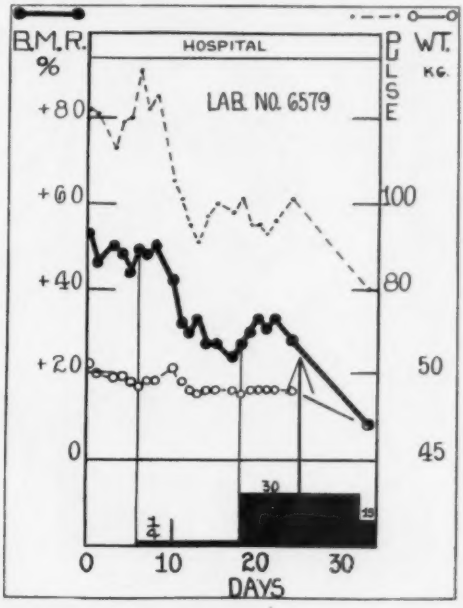

Chart 1.—Moderate reduction in basal metabolism during the administration of 1/4 drop of compound solution of iodine daily, with no further reduction during the administration of 30 drops daily, preceding a subtotal thyroidectomy for exophthalmic goiter. In this and subsequent charts the arrows denote subtotal thyroidectomies; the black areas represent periods of treatment with compound solution of iodine, and the figures above them the dosage in drops.

1/5 drop daily had produced its maximum effect, and plus 13 per cent after larger doses (from 1 to 30 drops daily) had produced their maximum effects. In the seven cases that showed a reduction of 10 points or more during the administration of 1/5 drop daily, the basal metabolism averaged plus 28 per cent before iodine was begun and plus 15 per cent after this dose had had its maximum effect. The

greatest drop recorded was 21 points (from plus 47 to plus 26 per cent). In chart 8 are given detailed data on an outpatient who showed practically a maximum reduction in basal metabolism on ⅕ drop daily. This was when the patient had thyrotoxicosis following a subtotal thyroidectomy. Before operation she had shown a marked reduction in basal metabolism on 1 drop daily (table 1 and chart 1 in the first paper of this series [1]).

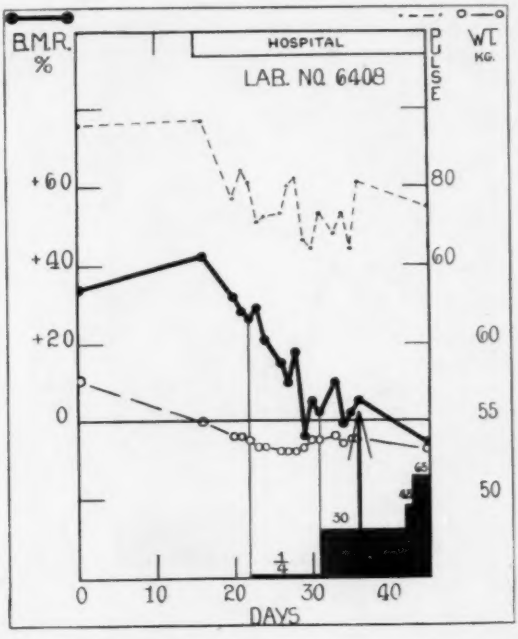

Chart 2.—A reduction in basal metabolism during the administration of ¼ drop of compound solution of iodine daily, with no further reduction during the administration of 30 drops daily, preceding a subtotal thyroidectomy for exophthalmic goiter.

TIME REQUIRED FOR MAXIMUM REDUCTION IN BASAL METABOLISM

The time required for maximum reduction in basal metabolism to occur could be adequately determined only in the house patients who received ¼ drop daily. In the seven cases that showed a drop of 10 or more points, the maximum reduction occurred in from three to seven days (five days, on the average). In one of these a drop was noted

within the first twenty-four hours, and in the others it first appeared within from two to four days. In those cases that responded, the average daily drop in the basal metabolic rate was 3.4 per cent—about the same as that in the ½ drop series and a little less than that for the 1 drop series.

COMPARISON OF EFFECTS OF THE ADMINISTRATION OF ONE-QUARTER AND ONE-FIFTH DROP OF COMPOUND SOLUTION OF IODINE DAILY WITH THOSE OF THE ADMINISTRATION OF ONE-HALF AND ONE DROP DAILY

In table 4 and chart 9 we have compared the effects on basal metabolism, of administering 1, ½ and ¼ drops, respectively, of com-

TABLE 4.—*Comparison of the Effect on Basal Metabolism of the Daily Administration of One Drop, One-Half Drop, One-Fourth Drop and One-Fifth Drop of Compound Solution of Iodine to Hospital Patients with Exophthalmic Goiter*

Series	Number of Cases	Average Basal Metabolic Rate, per Cent of Normal: On Admission	Resting Level	After Reaching a Level on Small Doses	After Reaching a Level on Larger Doses	On Small Doses: Greatest Drop in Basal Metabolic Rate, Points	Average Drop in Basal Metabolic Rate, Points	Average Total Drop in Basal Metabolic Rate on All Doses, Points	Average Daily Drop in Basal Metabolic Rate on Small Doses, Points
1 drop (all cases)	17	+60	+46	+19	....	49	27	..	...
1 drop (cases that responded)*	15	+64	+50	+19	....	49	31	..	4.4
1 drop (cases in which larger doses were given)	14	+62	+48	+19	+21	49	29	27	...
1 drop (cases that responded and that also were given larger doses)	12	+67	+52	+20	+22	49	32	30	...
½ drop (all cases)	20	+54	+40	+20	+21	40	14	19	...
½ drop (cases that responded)	13	+55	+42	+18	+17	40	24	25	3.4
¼ drop (all cases)	14	+62	+43	+34	+29	26	9	14	...
¼ drop (cases that responded)	7	+63	+42	+25	+21	26	17	21	3.4
⅕ drop (all cases)	2	+56	+47	+41	+42	14	6	5	...
⅕ drop (case that responded)	1	+51	+53	+39	+41	14	14	12	...

* A response means a drop of 10 points or more in the basal metabolic rate.

pound solution of iodine daily in three series of hospital patients with exophthalmic goiter. In all series the cases were unselected and the disease was of about the same general severity. All observations were made under approximately the same conditions. The results, therefore, are comparable. They show that:

1. The percentage of cases that responded was least in the ¼ drop series—50 per cent as compared with 65 per cent for the ½ drop series and 88 per cent for the 1 drop series.

2. The average response was least in the ¼ drop series—9 points (from plus 43 to plus 34 per cent) as compared with 14 points (from plus 40 to plus 26 per cent) in the ½ drop series and 27 points (from plus 46 to plus 19 per cent) in the 1 drop series.

3. When only the cases that showed a reduction in basal metabolism are considered in each series, the response was least in the ¼ drop series. Thus in this series, seven cases that responded showed an average reduction of 17 points (plus 42 to plus 25 per cent) in basal metabolism, whereas in the ½ drop series, the thirteen cases that responded showed an average reduction of 24 points (from plus 42 to plus 18 per cent), and in the 1 drop series, the fifteen cases that responded showed an average reduction of 31 points (from plus 50 to

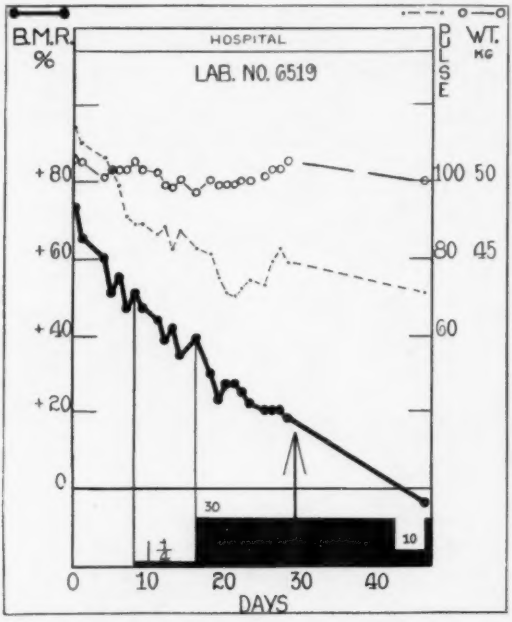

Chart 3.—A reduction in basal metabolism during the administration of ¼ drop of compound solution of iodine daily, with some further reduction during the administration of 30 drops daily, preceding a subtotal thyroidectomy for exophthalmic goiter.

plus 19 per cent). A relation between the amount of the reduction in basal metabolism and the size of the dose can be shown also in a few cases of the disease in which the preliminary administration of small doses did not completely interfere with the effect of larger doses subsequently administered. Thus case 5168 in table 3 showed no response on ⅕ drop, a moderate response on 1 drop and a maximum on 5 drops.

The foregoing comparison might not be considered entirely fair, as it means comparing seven cases in the ¼ drop series with thirteen in

the ½ drop series and fifteen in the 1 drop series. In only one, however, of the fifteen cases that responded in the 1 drop series did the basal metabolism drop less than 20 points. Thus, the average reduction of the seven cases in the 1 drop series that showed the smallest response (i. e., 10 or more points) is greater than the average for the seven of the ¼ drop series that responded. There can be little doubt, therefore, that there is a difference in the magnitude of the response in those

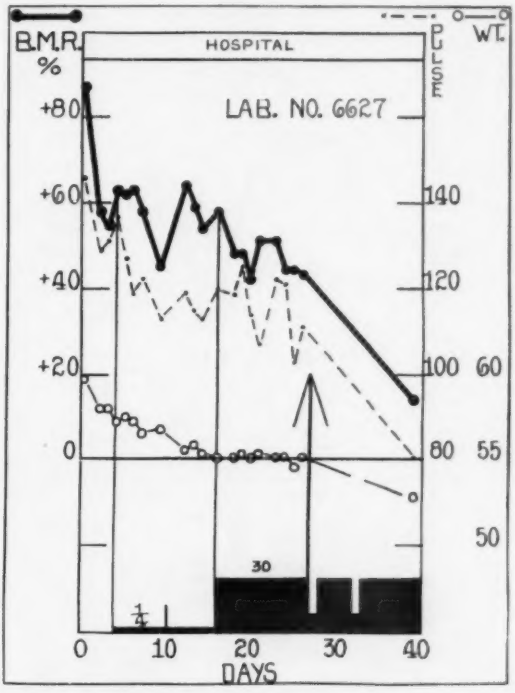

Chart 4.—No reduction in basal metabolism during the administration of ¼ drop of compound solution of iodine daily followed by a slight reduction during the administration of 30 drops daily, preceding a subtotal thyroidectomy for exophthalmic goiter.

that responded in the two series. This is also suggested by the fact that the greatest reduction in the 1 drop series was 49 points, in the ½ drop series 40 points, and in the ¼ drop series 26 points.

4. Not only was the response to ¼ drop less than that to ½ and 1 drop, but the total reduction in basal metabolism on all doses of iodine

was less in the ¼ drop series than in the other two. Thus, the effect of all doses in the ¼ drop series was to reduce the basal metabolic rate only 14 points (from plus 43 to plus 29 per cent), as compared with 19 points (from plus 40 to plus 21 per cent) in the ½ drop series and 27 points (from plus 48 to plus 21 per cent) in the 1 drop series. (This refers only to those patients who received large doses.)

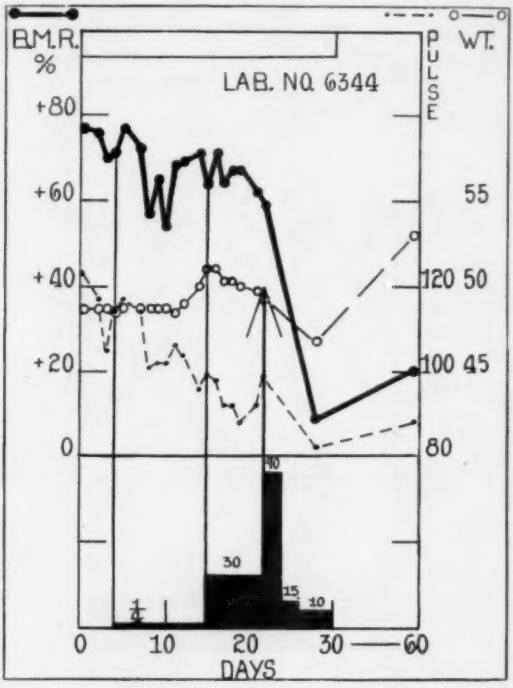

Chart 5.—No reduction in basal metabolism either during the administration of ¼ drop of compound solution of iodine daily or during the subsequent administration of 30 drops daily, preceding a subtotal thyroidectomy for exophthalmic goiter.

As previously pointed out, the difference between the effects of large doses in the ½ and 1 drop series could be accounted for by the fact that in the former the large doses were not given long enough to produce their maximum effects. The small effect of large doses in some of the cases in the ¼ drop series can perhaps be explained in a similar manner. It seems unlikely that it can be explained so simply in all of them, however. Thus, in the nine cases (6344, 6519, 6537,

6539, 6542, 6579, 6586, 6627 and 6634) in the ¼ drop series in which 30 drops a day were given for six to twelve days (average, eight days) immediately after the small dose, the results were no more satisfactory than in the cases in which the large dose was given for a shorter time. The average basal metabolic rate of these nine patients on admission was plus 68 per cent; the average resting rate was plus 49 per cent; after ¼ drop had been given daily for an average of eleven and one-half days it was plus 43 per cent, and on 30 drops a day it decreased

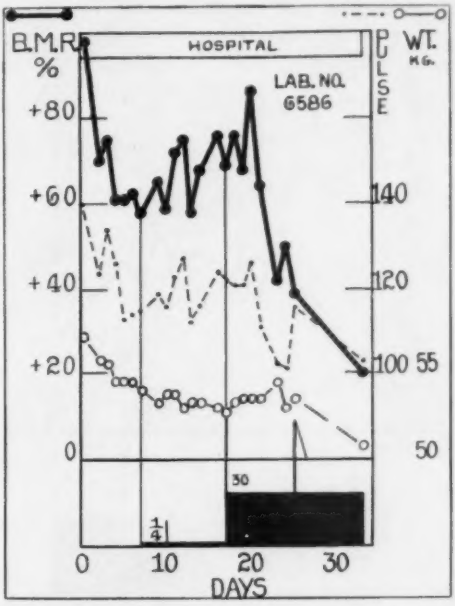

Chart 6.—A rise in basal metabolism and an increase in severity of exophthalmic goiter during the administration of ¼ drop of compound solution of iodine daily followed by a reduction in both factors during the administration of 30 drops daily, preceding a hemithyroidectomy (represented by half arrow).

only to plus 35 per cent. In seven of the cases (6344, 6413, 6423, 6537, 6542, 6586 and 6627) that showed no reduction in basal metabolism during the administration of ¼ drop, a reduction on 30 drops a day was noted only in two, and in these two it was not great. In these seven cases the large doses were given for an average of seven days after the small dose.

The conclusion is thus suggested that doses of iodine that are too small to affect the basal metabolism or that are so small as to have

only a slight effect, may in some way interfere with the effect of larger doses subsequently administered.[4]

Although the effect of ⅕ drop was observed on only two house patients, the data on them so far as they go, support this conclusion (table 1). It is doubtful whether the conclusion is upheld by the data on the outpatients who received ⅕ drop, and it does not appear to be upheld by the data thus far collected on the effect of administering ⅛ drop daily to house patients. The average reduction on all doses, in patients who received large doses, was roughly the same in both the

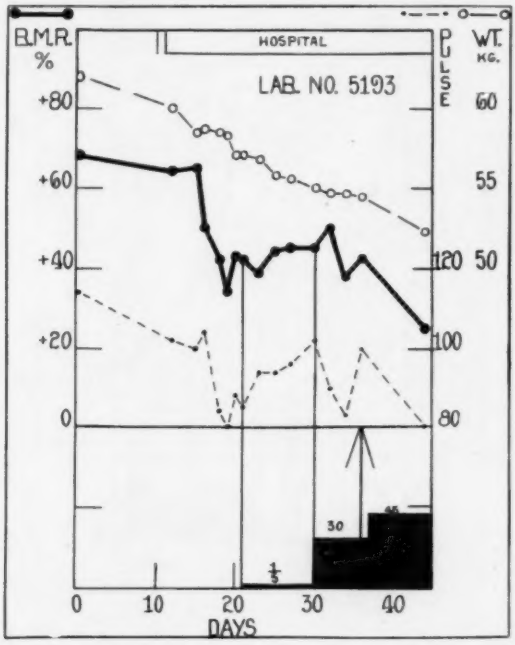

Chart 7.—No reduction in basal metabolism either during the administration of ⅕ drop of compound solution of iodine daily or during the subsequent administration of 30 drops daily, preceding a subtotal thyroidectomy for exophthalmic goiter.

4. To date, there has been one postoperative death in the patients in this study (no. 5850 of the ½ drop series). This patient died suddenly, about forty hours after an uneventful subtotal thyroidectomy. We consider it unlikely that the small dose given before the large dose was responsible for his death because, although his disease was initially severe, his basal metabolism dropped to plus 27 per cent on administration of iodine, and he appeared to be a satisfactory operative risk. The cause of death was undetermined but was thought to be a pulmonary embolus. We have not made a systematic study to determine whether the immediate postoperative reaction in these patients was more severe than that in a group of patients given large doses initially.

⅕ and the 1 drop series of outpatients (chart 10). Practically all the outpatients, however, had the disease in mild form. It has been our experience that such cases are in general more labile to iodine than are severe cases. Thus we held the disease in check for years in a small series of mild cases of the disease by the continuous administration of iodine, whereas in severe cases with similar medication, the disease practically always became worse—usually after a short period of "remission." [5]

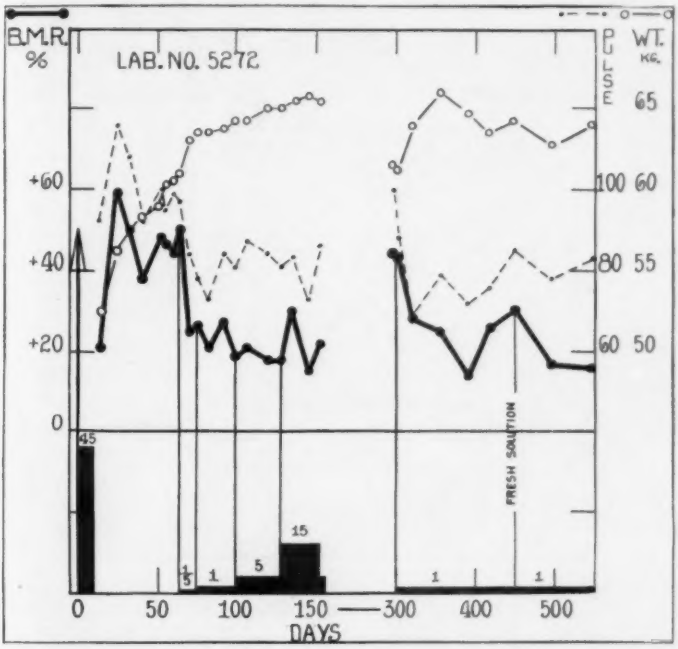

Chart 8.—Maximum reduction in basal metabolism during the daily administration of ⅛ drop of compound solution of iodine to a patient who had thyrotoxicosis following a subtotal thyroidectomy for exophthalmic goiter.

In six house patients in whom we have thus far observed the effect of the daily administration of ⅛ drop of compound solution of iodine, this small dose, while having little effect in itself, did not seem to interfere with the effect of the large dose given immediately afterward. Thus, the average basal metabolic rate on admission was plus 55 per cent; after a period of rest, it was plus 41 per cent; after ⅛ drop had

5. Thompson, W. O.; Thompson, P. K.; Brailey, A. G., and Cohen, A. C.: Some Experiences with the Prolonged Treatment of Exophthalmic Goiter by Iodine Alone, Arch. Int. Med., in press.

been given daily for an average of twelve days, it was plus 36 per cent; and on 30 drops a day, it dropped to plus 14 per cent. While the effect of large doses was observed for nine to sixteen days, or for an average of twelve days, the lowest level of metabolism during their administration appeared in from three to ten days, or in an average of six days. It thus appears unlikely that an inadequate period of observation could account for the small effect of large doses in the nine cases in the ¼ drop series in which their effect was noted for from six to twelve days (average, eight days). Although the patients in the ¼ drop series appeared, on the whole, to have the disease in more severe form than

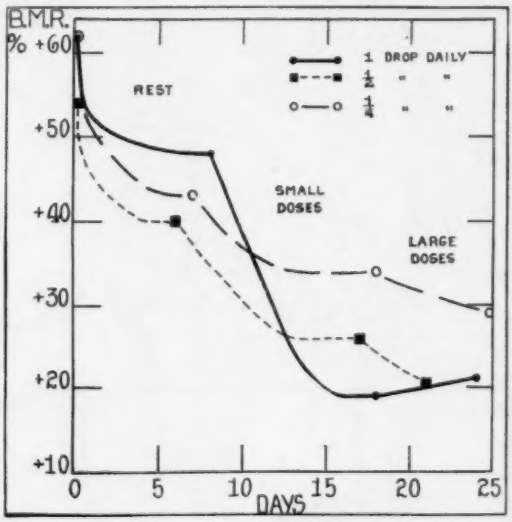

Chart 9.—A comparison of the effects on basal metabolism of the daily administration of 1, ½ and ¼ drop, respectively, of compound solution of iodine to three series of hospital patients. In each case the first point is the average of the basal metabolisms shortly after admission; the second point is the average resting level of metabolism; the third point is the average of the levels to which the metabolism fell during the administration of small doses (¼, ½ and 1 drop daily), and the fourth point is the average of the levels during the immediate subsequent administration of larger doses (usually 30 drops daily). Only those cases are considered in which the effect of larger doses was noted. The points are arbitrarily connected by curved lines, as these denote the true course of the basal metabolism more nearly than straight lines.

those thus far included in the ⅛ drop series, the reason for the difference in the response of these two series of patients to large doses is by no means clear. It is possible that the difference in the small doses of iodine may be important, and the ⅛ drop series is perhaps too small

at present to draw conclusions from. Then, of course, it must be recognized that the effect of giving large doses of iodine initially to these two groups of patients instead of preceding their administration by that of small doses, is unknown.

The effect of administering ⅕ drop of compound solution of iodine to outpatients is compared with that of administering 1 drop in table 5 and chart 10. In both groups, most of the patients had the disease in mild form, and the average level of basal metabolism was about the same in both before iodine was started. The metabolic rate decreased, on the average, only 8 points (from plus 32 to plus 24 per cent) on ⅕ drop, but it was reduced, on the average, 21 points (from plus 32 to plus 11 per cent) by 1 drop. The maximum reduction in the ⅕ drop series was 21 points (from plus 47 to plus 26 per cent) as compared

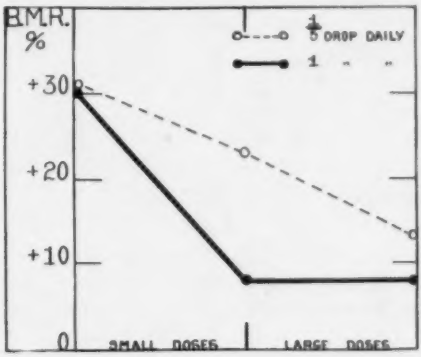

Chart 10.—A comparison of the effects on basal metabolism of the daily administration of 1 drop and ⅕ drop of compound solution of iodine to two series of outpatients.

with 44 points (from plus 72 to plus 28 per cent) in the 1 drop series. The difference is still striking if in each series only the cases are considered in which the metabolism dropped 10 points or more. In seven such observations on ⅕ drop, the basal metabolic rate was lowered, on the average, 13 points (from plus 28 to plus 15 per cent), whereas in twenty-three observations on 1 drop it was lowered, on the average, 26 points (from plus 33 to plus 7 per cent). In the 1 drop series no further lowering of the metabolism was usually noted when the dose of iodine was markedly increased, whereas in the ⅕ drop series it averaged 10 points lower on large doses.

The difference in effect between ⅕ drop and 1 drop of compound solution of iodine daily in the outpatients, merely serves to confirm the differences between the effects of ¼, ½ and 1 drop in the three series of house patients.

COMMENT

From the data presented, it is obvious that the effect of iodine on the basal metabolism in exophthalmic goiter is not of the all-or-none type, but that it is related within certain limits to the size of the dose. In most cases seen in this hospital, the minimum amount of iodine that will produce a maximum reduction in basal metabolism is about 6 mg. per day, whereas the smallest dose that will produce any reduction is a little greater than 1.5 mg. per day in about 50 per cent of the cases. As the upper and lower limits vary considerably from case to case, the actual range in many instances is probably somewhat less than the foregoing figures would indicate.

TABLE 5.—*Comparison of the Effect on Basal Metabolism of the Daily Administration of One Drop and of One-Fifth Drop of Compound Solution of Iodine to Outpatients with Exophthalmic Goiter*

Series	Number of Observations	Average Basal Metabolic Rate, per Cent of Normal			On Small Doses		Average Total Drop in Basal Metabolic Rate on All Doses, Points
		Before Treatment	After Reaching a Level on Small Doses	After Reaching a Level on Large Doses	Greatest Drop in Basal Metabolic Rate, Points	Average Drop in Basal Metabolic Rate, Points	
1 drop (all cases)	28	+32	+11	....	44	21	..
1 drop (cases on larger doses)	15	+30	+ 8	+ 8	44	22	22
1 drop (all cases that responded)*	23	+33	+ 7	....	44	26	..
1 drop (all cases that responded and also had larger doses)	13	+31	+ 6	+ 6	44	25	25
1/5 drop (all cases)	16	+32	+24	....	21	8	..
1/5 drop (cases on larger doses)	13	+31	+23	+13	21	8	18
1/5 drop (all cases that responded; all had larger doses)	7	+28	+15	+ 2	21	13	20

* A response means a drop of 10 points or more in the basal metabolic rate.

It is well known that typically, the reduction in basal metabolism during the administration of iodine in exophthalmic goiter is accompanied by a storage of colloid and an increase in the size of the thyroid gland.[6] It would appear reasonable to try to find some correlation between the amount of iodine necessary to cause a marked storage of colloid and the amount necessary to cause a maximum reduction in

6. Marine, D., and Lenhart, C. H.: Pathological Anatomy of Exophthalmic Goiter: The Anatomical and Physiological Relations of the Thyroid Gland to the Disease; the Treatment, Arch. Int. Med. **8**:265 (Sept. 15) 1911. Cattell, R. B.: The Pathology of Exophthalmic Goitre: A Histological and Chemical Study of the Changes Following the Administration of Iodin (Lugol's Solution), Boston M. & S. J. **192**:989, 1925. Rienhoff, W. F., Jr.: The Histological Changes Brought About in Cases of Exophthalmic Goiter by the Administration of Iodine. Bull. Johns Hopkins Hosp. **37**:285, 1925.

basal metabolism. In a consideration of our data from this point of view it must be recognized that there are at least three unknown quantities: (1) the amount of iodine excreted unused on the doses given, (2) the amount of iodine present in the gland before treatment was started and (3) the capacity of the gland to store iodine.

There is some evidence bearing on these three points. Marine [7] has presented data which suggest that when a small amount of iodine is administered, a large part of it may be absorbed by the thyroid gland. When a great excess is given, however, most of it is eliminated in the urine within twenty-four hours (Cattell [8] and Greenbaum, and Raiziss [9]). In the literature there are a few reports on the iodine content of exophthalmic goiter glands from patients who had been operated on without receiving iodine, as compared with those who had received iodine.[10]

From the weight of the portion of gland removed at operation and the fraction that this formed of the whole gland, it is possible to calculate roughly the weight of the thyroid at the time of operation. The average weight of the whole gland in thirty-two of our cases (all four series of house patients) was thus calculated to be about 82 Gm.[11] Marine and Lenhart,[12] in Cleveland, found an average iodine content of 1.14 mg. per gram of dried gland in fifty-eight patients with exophthalmic goiter who did not receive iodine, and an average of 3.08 mg. per gram in eight patients who received iodine. Before the days of iodine medication in exophthalmic goiter, Wilson and Kendall [13] found an average iodine content of 0.96 mg. per gram of dried gland in one

7. Marine, D.: Etiology and Prevention of Simple Goiter, Medicine **3**:453, 1924.

8. Cattell, R. B.: The Elimination of the Iodine in the Urine in Normal Persons and in Exophthalmic Goiter, Boston M. & S. J. **195**:69, 1926.

9. Greenbaum, F. R., and Raiziss, G. W.: Elimination of Iodine After Oral or Intravenous Administration of Various Iodine Compounds in Single Massive Doses, J. Pharmacol. & Exper. Therap. **30**:407, 1927.

10. Marine and Lenhart (footnote 6, first reference). Cattell (footnote 6, second reference). Wilson, L. B., and Kendall, E. C.: The Relationship of the Pathological Histology and the Iodin Compounds of the Human Thyroid, Am. J. M. Sc. **178**:79, 1916. Weir, J. F.: The Thyroxin and Tryptophane Content of the Diseased Thyroid Gland, and the Iodin Compounds in Desiccated Thyroid, Am. J. M. Sc. **169**:860, 1925.

11. It is perhaps best from the point of view of the general problem to take the average of all glands weighed, because in the 1 drop series several of the lighter glands were not weighed and in the ¼ drop series two of the heavier ones were not. (If all thyroid glands in all series had been weighed, the average weight for each series would have been more nearly equal.)

12. Marine and Lenhart (footnote 6, first reference).

13. Wilson and Kendall (footnote 10, third reference).

hundred and thirty-seven cases at the Mayo Clinic. After iodine was introduced, Weir,[14] working at the same Clinic, found an average iodine content of 2.58 mg. per gram in twenty-four cases. The corresponding figures reported by Cattell [15] from the Lahey Clinic in Boston are 2.1 mg. (fourteen cases) and 4.2 mg. (sixteen cases), respectively. Assuming the ratio of dry to wet weight to be about one-fifth, the thyroid glands of our patients, on the basis of the figures of Marine and Lenhart, would have contained 18.7 mg. of iodine before medication was started and 50.5 mg. after iodine was administered—a difference of 31.8 mg.; on the basis of the figures reported from the Mayo Clinic, 15.7 mg. and 42.3 mg., respectively—a difference of 26.6 mg.; and on the basis of Cattell's figures, 34.4 mg. and 68.9 mg., respectively—a difference of 34.5 mg. In our 1 drop series, 42 mg. of iodine were supplied to each patient in seven days—the average time required for a maximum reduction in basal metabolism to appear. During the same time, on a daily dose of ½ drop and ¼ drop of compound solution of iodine, only 21 mg. and 10.5 mg. of iodine, respectively, were supplied to each patient. Thus, in seven days on the smaller doses (½ and ¼ drop), sufficient iodine was not supplied for the maximum storage of colloid even if it could all be used for that purpose. Moreover, even on these small doses it seems probable that some iodine would be eliminated unused. The actual portion of them that would be utilized is unknown, but it is doubtful if, on 1 drop a day, it would be any larger than the minimum required for maximum storage.

The reason for the maximum effect of 1 drop and the less marked effect of smaller doses, therefore, may be that 1 drop a day is roughly about the minimum dose that enables the gland in most cases to store colloid at an adequate rate. It is thus of interest that the few patients who showed a reduction in basal metabolic rate during the administration of ¼ drop daily had the disease in mild form. It is at present unknown, of course, whether it is necessary to have a maximum storage of colloid in order to have a maximum reduction in basal metabolism.

A further analysis of the data suggests that the smaller the gland the less the amount of iodine required to produce a reduction in basal metabolism. Whereas two patients, whose thyroid glands weighed more than 200 Gm., showed a well marked reduction in basal metabolism during the administration of 1 drop of compound solution of iodine daily, no patient whose thyroid weighed more than 84 Gm. showed a reduction in basal metabolism during the administration of ½ drop a day, and no patient whose thyroid weighed more than 34 Gm. showed a reduction during the administration of ¼ drop a day (except one

14. Weir (footnote 10, fourth reference).

15. Cattell (footnote 6, second reference).

whose thyroid weighed 154 Gm. and whose metabolism dropped only 10 points).

A similar conclusion is suggested by table 6. Thus, if all ½ drop cases in which the gland was weighed are considered, the average theoretical maximum amount of iodine available for the storage of colloid (the amount of iodine administered plus the iodine content of the gland before medication was started) was considerably less than the amount which the gland could hold. The reduction in basal metabolism was correspondingly small—only 10 points (from plus 39 to plus 29 per cent). On the other hand, in the seven cases in the ½ drop series in which the thyroid was weighed and a reduction in basal metabolism was noted, the theoretical amount of iodine available for the storage of colloid more nearly approached the amount that the gland could hold. In these cases the average reduction in basal metabolism was well marked—23 points (from plus 39 to plus 16 per cent). A similar situation existed in the ¼ drop series.

While the average weight of the glands in the 1 drop series was greater than that of the glands in the ½ and ¼ drop series, the theoretical amount of iodine available for the storage of colloid was proportionately greater in the 1 drop series than in the other two, and the average reduction in basal metabolism was correspondingly greater. In the four cases in the ¼ drop series in which the weight of the thyroid was determined and in which there was a reduction of basal metabolism of more than 10 points, the ratio of iodine available for colloid storage to the amount of iodine that the gland could hold was less than in the 1 drop series, and the reduction in basal metabolism was also less.

There are, however, certain discrepancies when an attempt is made to explain the reduction in basal metabolism entirely on the basis of storage of colloid. In the two cases in the ½ drop series in which the thyroid weighed over 80 Gm. (actual weights, 81 and 84 Gm.) and a well marked reduction in basal metabolism occurred, and in the two cases in the 1 drop series in which the thyroid weighed more than 200 Gm. and a reduction in basal metabolism occurred, the amount of iodine supplied to the patients on the small dose regimens would certainly not have been adequate to cause a maximum storage of colloid unless the iodine content of the gland had been high before medication was started. Moreover, the reduction in basal metabolism presumably can begin before much colloid is stored; e. g., in five patients of the 1 drop series, four of the ½ drop series and one of the ¼ drop series, it had started within twenty-four hours. Some of these patients had large thyroid glands. It would thus appear that the output of thyroxin is sometimes diminished before sufficient colloid can be stored to produce a mechanical

TABLE 6.—*Summary of Relationship Between the Estimated Iodine Capacity of the Thyroid and the Theoretical Amount of Iodine Available for Storage (of Colloid) by This Gland on the Various Doses Administered*

	Number of Cases	Average Weight of Thyroid Gland, Gm.	Average Time Required for Maximum Reduction in Basal Metabolic Rate, Days	Amount of Iodine Administered in Each Case in Time Required for Maximum Drop, Mg.	Possible Iodine Content of Thyroid Glands in Our Series: On Basis of Figures of Marine and Lenhart — Before Iodine Medication, Mg.	On Basis of Figures of Marine and Lenhart — After Iodine Medication, Mg.	On Basis of Figures of Marine and Lenhart — Sum of Iodine Administered and Iodine in Gland Before Medication, Mg.	On Basis of Mayo Clinic Figures — Before Iodine Medication, Mg.	On Basis of Mayo Clinic Figures — After Iodine Medication, Mg.	On Basis of Mayo Clinic Figures — Sum of Iodine Administered and Iodine in Gland Before Medication, Mg.	On Basis of Cattell's Figures — Before Iodine Medication, Mg.	On Basis of Cattell's Figures — After Iodine Medication, Mg.	On Basis of Cattell's Figures — Sum of Iodine Administered and Iodine in Gland Before Medication, Mg.	Average Basal Metabolic Rate, per Cent of Normal — Before Iodine Medication	Average Basal Metabolic Rate, per Cent of Normal — After Iodine Medication	Drop in Basal Metabolic Rate, Points
All 1 drop cases in which thyroid was weighed; all responded to iodine	8	111	7	42	25.3	68.3	67.3	21.4	57.3	63.4	46.6	93.2	88.6	+51	+18	33
All ½ drop cases in which thyroid was weighed	12	77	7	21	17.6	47.4	38.6	14.8	39.7	35.8	32.3	64.7	53.3	+39	+28	11
All the foregoing ½ drop cases that responded to iodine	8	49	6	18	11.2	30.2	29.2	9.4	25.3	27.4	20.6	41.2	38.6	+41	+18	23
All ¼ drop cases in which thyroid was weighed	11	57	5	7.5	13.0	35.1	20.5	10.9	29.4	18.4	23.9	47.8	31.4	+42	+33	9
All the foregoing ¼ drop cases in which the basal metabolic rate dropped 10 or more points on iodine	5	54	4	6.0	12.3	33.3	18.3	10.4	27.8	16.4	22.7	45.3	28.7	+41	+24	17
All the foregoing ¼ drop cases in which the basal metabolic rate dropped more than 10 points *	4	29	4	6.0	6.6	17.9	12.6	5.6	15.0	11.6	12.2	24.4	18.2	+40	+21	19
The ⅛ drop case in which thyroid was weighed	1	200	1	1.2	45.6	123.2	46.8	38.4	113.2	39.6	84.0	168.0	85.2	+53	+39	14

* These two subdivisions of the ¼ drop data are made because, by including among those that responded to iodine, the one case (no. 6539) in which the thyroid weighed 154 Gm. and in which the metabolism dropped only 10 points on ¼ drop, the average weight of the thyroid in such cases is practically doubled (54 instead of 29 Gm.), and the difference between the iodine capacity of the gland and the theoretical amount of iodine available for storage (of colloid) is markedly increased.

blocking of the secretion according to Marine's theory.[16] These considerations have led us to wonder whether storage of colloid is the cause of, or merely an accompaniment of, the fundamental change which iodine produces in the thyroid gland of exophthalmic goiter.

It is impossible to determine whether, when a reduction in basal metabolism occurs, any of the iodine administered is utilized in the elaboration of thyroxin. It is conceivable, however, that when the disease is acting with great intensity, the thyroid may thus utilize so much iodine that 1 drop daily is not sufficient to cause an adequate storage of colloid and, therefore, does not produce a maximum effect. It is doubtful if in exophthalmic goiter there is ever produced an excess of thyroxin which requires more than 6 mg. of iodine daily in its elaboration (at least thirty-eight times the daily output of a normal thyroid gland). In support of this is the fact that we have not yet observed a patient who failed to show some response to a dose of 1 drop daily that showed any response to any dose. Thus, on theoretical grounds, we doubt if the dose required to produce a maximum effect is ever greater than 5 drops of compound solution of iodine daily, and it may be less than this in all cases.

As the daily amount of iodine necessary to keep the thyroid gland of a normal man in a healthy state is probably much less than 0.16 mg. per day,[1] the amount that must be supplied to a patient with exophthalmic goiter before any reduction in basal metabolic rate will occur (a little over 1.5 mg. in about 50 per cent of the cases) is greater than would be necessary to supply a marked excess of thyroxin, if it were all utilized for that purpose. Our data thus suggest that iodine must be supplied to the thyroid faster than it can be utilized in the elaboration of thyroxin in order to produce the functional change that is associated with the storage of colloid and a decrease in the output of the hormone. Whether or not the thyroid can utilize iodine to form a still greater excess of thyroxin when it is not given fast enough to cause a storage of colloid is a difficult problem. From this standpoint, the increase in basal metabolism in two of the cases in our ½ drop series (charts 5 and 6 in the second paper of this series[2]) and in one of the cases in our ¼ drop series (chart 6) is of interest. In these three cases, the

16. Marine, D.: Iodin in the Treatment of Diseases of the Thyroid Gland, Medicine **6**:127, 1927. While Marine and Rogoff (J. Pharmacol. & Exper. Therap. **9**:1, 1916-1917) have shown that an increased deposit of colloid can be detected in the thyroid glands of normal animals as early as twenty hours after the administration of a single large dose of iodine, 1.5 to 6 mg. of iodine is probably inadequate to cause enough storage of colloid to produce "pressure retention," even if all of it could be used for this purpose within twenty-four hours. It may be maintained, of course, that a sudden small increase in the amount of colloid is sufficient to initiate the change.

reaction to iodine appeared to be reversible, the administration of small doses being associated with an increase in the basal metabolism and severity of the disease, and the immediate subsequent administration of large doses being associataed with a decrease in both factors. The rise and fall corresponded so well with the administration of small and large doses of iodine, respectively, that it seems unlikely that the phenomenon can be explained entirely on the basis of the spontaneous course of the disease. It is of interest that in all three cases the thyroid gland was large, the weight varying from 107 to 164 Gm.

It would not be surprising if in cases in which the cause of the disease is acting with great intensity, the gland could use as much as 3 mg. of iodine daily in the elaboration of thyroxin. If this explanation is correct, it may seem peculiar that more of the cases that did not show a reduction in basal metabolism in the two series, did not show a rise. There are at least three possible explanations for this: 1. It may be necessary to administer the iodine at a time when the disease is set to increase in severity spontaneously.[17] 2. In most of the cases the gland may have been secreting thyroxin at a maximum rate regardless of the iodine intake, salvaging, if necessary, the iodine atoms from the breakdown of thyroxin. 3. Sufficient time may not have elapsed for the extra thyroxin that could be produced to affect the metabolism. In a period of ten days in the ¼ drop series, 15 mg. of iodine would be the maximum available for the production of thyroxin. If all of this iodine could be utilized without loss in the elaboration of thyroxin, 23 mg. of the hormone would be produced. It would not be surprising if in some cases longer than ten days is necessary for 2.3 mg. of thyroxin daily to affect the basal metabolism when it is already high. While this is a plausible explanation for the cases in the ¼ drop series, it is doubtful if it is adequate to explain the lack of increase in the cases in the

17. Observations that we made on the effect of the prolonged treatment of the disease with iodine alone (footnote 5) have led us to believe that the rôle of iodine during an increase in the severity of exophthalmic goiter may be in large part a passive one, the iodine administered representing an excess of one of the raw materials out of which a still greater excess of thyroxin may be made. The idea that the spontaneous course of the disease is the most important thing in determining variations in the response of patients with exophthalmic goiter to iodine was expressed in an article by Means, Thompson and Thompson (Tr. A. Am. Phys. **43**:146, 1928) and by Means and Richardson (Diseases of the Thyroid, New York, Oxford University Press, 1929, p. 151). We have also noted, however, that during the continuous administration of iodine its effect may wear off at least in part. Thus, in the presence of an excess of this element, it would often appear that some reaction occurs which tends to counteract its beneficial effect. This phenomenon corresponds so closely with the administration of iodine that it seems unlikely that it can be explained satisfactorily by the spontaneous course of the disease. We therefore think it unwise to consider that the rôle of iodine during such an increase in the severity of exophthalmic goiter is entirely passive.

½ drop series, in which a possible maximum of 4.6 mg. of thyroxin daily could be produced from the iodine administered.

It is of some interest that in the cases which responded in the ¼ drop and in the ½ drop series, the maximum reduction in basal metabolism occurred just as quickly as in the 1 drop series. It occurred in five days on the average in the ¼ drop series and in seven days in the ½ and 1 drop series. Thus, it may be seen from table 4 that the average daily rate of reduction in basal metabolism in the cases that responded was 4.4, 3.4 and 3.4 points, respectively, for the 1, ½ and ¼ drop series. It seems surprising, perhaps, that on the smaller doses the slower rate of reduction did not persist for a longer time, so that the total reduction would equal that on 1 drop daily. Not only did this fail to occur, but, as previously stated, large doses given immediately after the small doses sometimes caused no further reduction in basal metabolism. It was chiefly for this reason that 17 per cent of our house patients (including all four series) showed no reduction in basal metabolism on any dose of iodine. This is about twice as great as the percentage of cases that show no response during the initial administration of large doses. The ¼ drop series was responsible for four of the nine failures. In this series only 71 per cent of the cases responded even to large doses. Why the temporary administration of ½, ¼ or ⅕ drop daily, even if not effective itself, should sometimes interfere with the effect of large doses given immediately afterward, is not clear. It is possible that the small doses in some way allow the gland to adjust itself to the effect of iodine before the large doses are given. The fact that in three of the cases in the 1 drop series and in two of those in the ½ drop series, the basal metabolism started to rise a little after showing its maximum drop and that this slight rise continued after large doses were given, thus takes on added significance. The observation that small doses sometimes interfere with the effect of large doses is of interest in connection with the impression of several observers that iodized salt aggravates the disease.[18] From the foregoing considerations it would appear that the real test of whether the reduction of the basal metabolism on 1 drop of compound solution of iodine daily is maximum, is a comparison of its effect with that of larger doses given in other groups of patients, and not with that of larger doses given immediately afterward. This has a general application to all data on iodine. The effects of various doses can be compared only by giving each dose to untreated patients with the disease under the same conditions.

18. Hartsock, C. L.: Iodized Salt in the Prevention of Goiter: Is It a Safe Measure for General Use? J. A. M. A. **86**:1334 (May 1) 1926. Hutton, J. H.: Dangers of Iodine in Treatment of Goiter, Illinois M. J. **50**:408, 1926. Holmes, M. E.: The Value and Danger of Iodine in Thyroid Disease, New York State J. Med. **27**:538, 1927.

From the standpoint of patients with exophthalmic goiter, the results indicate that the indiscriminate use of iodine in any form in the treatment of goiter is probably harmful.

Most of our patients lived within 100 miles of Boston. At present, therefore, our results can be said to apply only to patients in this locality. Many observers are of the opinion that the disease is more intense in goitrous regions (notably in the Great Lakes region) than here. This impression has not yet been corroborated by well controlled data. If it is correct, it also may be true that the minimum dose of iodine necessary to produce a maximum effect is greater in goitrous regions.

SUMMARY

During the daily administration of ¼ drop of compound solution of iodine to fourteen unselected hospital patients with exophthalmic goiter, seven showed a reduction in basal metabolism of from 10 to 26 points, six showed no significant change and one showed an increase. During the administration of ⅕ drop daily to two hospital patients with the disease, one showed a reduction of 14 points and the other showed no change.

In the ¼ drop series, the basal metabolism was only slightly lower, and in the two hospital patients who received ⅕ drop, no lower during the subsequent administration of 30 drops a day, than during the administration of the small doses.

Whereas only 50 per cent of the patients showed a reduction in basal metabolism of 10 points or more during the daily administration of ¼ drop, 65 per cent showed a reduction during the daily administration of ½ drop, and 88 per cent during the daily administration of 1 drop.

The administration of ¼ drop a day caused an average reduction in basal metabolism of only 9 points (from plus 43 to plus 34 per cent) as compared with 14 points (from plus 40 to plus 26 per cent) for ½ drop and 27 points (from plus 36 to plus 19 per cent) for 1 drop.

In the seven patients who responded to ¼ drop, the maximum reduction in basal metabolism occurred on the average in five days. In one patient it had started within twenty-four hours.

In a series of outpatients, most of whom had the disease in a mild form, the daily administration of ⅕ drop produced an average reduction in basal metabolism of only 8 points (from plus 32 to plus 24 per cent) as compared with 21 points (plus 32 to plus 11 per cent) for 1 drop. Large doses given immediately after ⅕ drop caused a lowering of the metabolism to nearly the same level as 1 drop given initially in the second series.

CONCLUSIONS

The effect of iodine in exophthalmic goiter is not of the all-or-none type, but it is related within certain limits to the size of the dose.

In most of the cases in this hospital, the minimum dose that will produce a maximum reduction in basal metabolism is about 6 mg. of iodine per day. In about 50 per cent of the cases the smallest dose that will produce any effect is greater than 1.5 mg. per day. In 50 per cent of the cases it is 1.5 mg. per day or less.

It would appear that in exophthalmic goiter, iodine must be supplied to the thyroid gland faster than it can be utilized in the elaboration of thyroxin, in order to cause the functional change that is associated with the storage of colloid, and a decrease in the output of thyroxin.

The onset of a reduction in basal metabolism within twenty-four hours after the administration of as little as from 1.5 to 6 mg. of iodine in ten cases, suggests that the output of the thyroid sometimes may be diminished before sufficient colloid can be stored to cause a blocking of the secretion.

In three of the cases observed, the reaction to iodine appeared to be reversible, the administration of ¼ to ½ a drop of compound solution daily being associated with an increase in the basal metabolism and in the severity of the disease, and the immediate subsequent administration of large doses being associated with a decrease in both factors.

Doses as small as ¼ and ½ drop of compound solution of iodine a day, even when they are too small to cause a reduction in basal metabolism, may sometimes interfere with the effect of much larger doses given immediately afterward. In mild cases of the disease, this phenomenon does not seem to occur.

A comparison of the effects of various doses of iodine, therefore, can be made only by giving each dose to untreated patients with the disease. It is also essential to secure a resting level of basal metabolism before iodine is started.

In the routine preoperative treatment of exophthalmic goiter it is desirable to give suddenly an adequate excess of iodine and not to precede this with small doses.

THE RESPONSE OF THE RETICULOCYTES IN SECONDARY ANEMIAS FOLLOWING VARIOUS FORMS OF TREATMENT *

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In recent years, the reticulated erythrocytes in the circulating blood have attracted considerable attention in the study of various anemias. This has been particularly true since Minot and Murphy [1] pointed out that when patients with pernicious anemia were fed large amounts of liver there was a rapid increase in the production of hemoglobin, erythrocytes and reticulocytes. The increase in the reticulated red blood cells was taken as evidence of the efficiency of liver treatment, and their appearance in the circulating blood as an indication of an active production of red blood cells. During the past year, we have been interested in the reticulocyte response in the various forms of secondary anemia, following different kinds of treatment, and in this essay we propose to present the results of a study of fifty-three cases.

LITERATURE

Before presenting the details of our studies, we shall summarize rather briefly the present knowledge regarding these cells. We shall make no attempt to review the enormous literature on this subject since there have been several recent summaries. The essay of Seyfarth [2] may be consulted for details and an excellent bibliography.

It is generally accepted that the reticulocytes are young and immature red blood cells. Their presence in the circulating blood in numbers above 1 per cent of the total erythrocytes is considered an increase above normal and an indication of increased activity on the part of the bone-marrow. The nature of the reticulum is unknown, but the consensus seems to be that it is derived from the protoplasm of the cell rather than from the nucleus. This has been emphasized recently by Seyfarth,[2] Cooke [3] and others. Cooke [3] is of the opinion that the

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1. Minot, G. R., and Murphy, W. P.: Treatment of Pernicious Anemia by a Special Diet, J. A. M. A. **87**:470 (Aug. 14) 1926; A Diet Rich in Liver in the Treatment of Pernicious Anemia, J. A. M. A. **89**:759 (Sept. 3) 1927.

2. Seyfarth, Caryl: Experimentelle und klinische untersuchungen über die vitalfärbbaren Erythrozyten, Folia haemat. **34**:7, 1927.

3. Cooke, W. E.: The Artificial Production of Punctate Basophilia and Reticulation in Erythrocytes, Am. J. M. Sc. **177**:537, 1929.

reticulum is probably a hemoglobin compound and qualitatively the same as basophilic stippling and polychromasia.

Reticulocytes in the Normal Circulating Blood.—In adults, the number of vitally stained cells in the circulating blood varies from 0.2 per cent to 1 per cent. Seyfarth and Jurgens [4] showed that in normal infants at birth the reticulocytes number approximately 7 per cent. Following birth, the number decreases rapidly, so that by the sixth week the average count is only 0.7 per cent. In premature infants at birth, the reticulocytes are between 10 and 30 per cent, and the percentage decreases more slowly than in normal infants. Following the sixth week of extra-uterine life, the reticulocytes are not increased above 1 per cent, except under certain physiologic or pathologic circumstances.

Different animals vary in the number of reticulocytes they have normally. Seyfarth [2] stated that the normal count for horses, sheep, hogs, cats and cows is between 0.1 and 0.2 per cent, and for dogs between 0.2 and 0.5 per cent. Smaller animals have higher counts. Guinea-pigs have between 0.5 and 5 per cent; rats, from 3 to 5 per cent; mice, from 4 to 6 per cent, and rabbits from 3 to 8 per cent. Young animals have more reticulocytes than old ones. It is also known that the number of reticulocytes in animal embryos may be high. In mice embryos, they vary between 30 and 40 per cent. Seyfarth and Jurgens [4] were able to show that at some time during embryonic life, all the red cells had reticulum. This observation, together with the fact that there was an abundant reticulum in many cells with a perfectly normal nucleus, led them to the conclusion that the reticulum was a part of the protoplasm and was not derived from the nucleus. Furthermore, reticulum was present in every cell containing hemoglobin at some time during its development. This view was supported by the work of Cooke,[3] who was able to produce reticulation artificially in any red cell without a nucleus. He expressed the opinion that the reticulum was probably a hemoglobin compound which was able to take up the stain because of an alteration in the red cell membrane.

Vitally stained red cells have been described as occurring in various numbers in different diseases in which the hematopoietic system is involved. These conditions may be reviewed as follows:

Reticulocytes in Pathologic States.—The percentage of reticulocytes may be markedly increased in malaria, hemolytic jaundice, posthemorrhagic anemias and anoxemia, and following the intravenous injection of distilled water into animals and following chemical intoxi-

4. Seyfarth, Caryl and Jurgens, R.: Untersuchungen über das Verhalten der vitalgranulierten roten Blutzellen (Reticulocyten) bei Embryonen und Neugebornen, Virchows Arch. f. path. Anat. **266**:676, 1927-1928.

cation such as phenylhydrazine poisoning. There may be a slight increase in their percentage in leukemia, Hodgkin's disease, carcinomatosis of the bone-marrow, kala-azar and chlorosis. In other conditions, such as aplastic anemia, the count is constantly low.

During recovery from various anemias, the percentage of reticulocytes may increase spontaneously. This is true during spontaneous recovery in acute posthemorrhagic anemias, pernicious anemia, malaria and the anemias following blood destruction, of which phenylhydrazine intoxication is an example.

The percentage of reticulocytes is also increased in some anemias, following various forms of treatment: following transfusion in pernicious anemia [5] and posthemorrhagic anemia; following splenectomy in splenic anemia [6] and pernicious anemia; [5] following ergosterol in the anemia of dogs after bile fistulas; [7] following cod-liver oil and high caloric diet in the anemia associated with dysentery; [8] following high liver feeding in pernicious anemia,[1] sprue,[9] anemia due to tapeworm,[10] anemia due to hookworm,[11] the anemias of pregnancy,[12] and the anemias of undernutrition, [11 12] and of carcinoma of the stomach; [13] following iron in splenic anemia, chlorosis and the anemia of dysentery [11]; following liver extract in pernicious anemia,[14] sprue,[15 16 17] the anemia due

5. Minot, G. R., and Lee, R.: Treatment of Pernicious Anemia, Especially by Transfusion and Splenectomy, Boston M. & S. J. **177**:761, 1917.

6. Dameshek, W.: The Reticulated Red Cells, Their Clinical Significance: Boston M. & S. J. **194**:759 (April 29) 1926.

7. Seyderhelmn, R., and Tammann, T.: Die Bedeutung der Galle für die Blutmauserung, Klin. Wchnschr. **6**:1177 (June 18) 1927.

8. Berglund, H.; Keefer, C. S., and Yang, C. S.: Deficiency Anemia in Chinese, Responding to Cod Liver Oil, Proc. Soc. Exper. Biol. & Med. **26**:418, 1929.

9. Bloomfield, A. L., and Wyckoff, H. A.: Remission in Sprue Following High Liver Diet: Case Report, California & West. Med. **27**:659, 1927.

10. Isaacs, R.; Sturges, C. C., and Smith, M.: Tapeworm Anemia, Arch. Int. Med. **42**:313 (Sept.) 1928.

11. Keefer, C. S., and Yang, C. S.: The Value of Liver and Iron in the Treatment of Secondary Anemia, J. A. M. A. **93**:575 (Aug. 24) 1929.

12. Minot, G. R.; Murphy, W. P., and Stetson, R. P.: The Response of the Reticulocytes to Liver Therapy: Particularly in Pernicious Anemia, Am. J. M. Sc. **175**:581, 1928.

13. Heath, E. H.: Personal communication to the authors.

14. Minot, G. R.; Cohn, E. J.: Murphy, W. P., and Larson, H. A.: Treatment of Pernicious Anemia with Liver Extract: Effects Upon the Production of Immature and Mature Red Blood Cells, Am. J. M. Sc. **175**:599, 1928.

15. Bloomfield, A. L., and Wyckoff, H. A.: The Treatment of Sprue with Liver Extract (343), Am. J. M. Sc. **177**:209, 1929.

16. Ashford, B. K.: Evaluation of Liver Extract in Treatment of Anemias of Sprue; Preliminary Note, J. A. M. A. **91**:242 (July 28), 1928.

17. Richardson, W., and Klumpp, T. G.: Sprue; Case Treated with Authorized Liver Extract Effective in Pernicious Anemia, New England J. Med. **199**:215 (Aug. 2) 1928.

to tapeworm,[18] and the anemias of childhood;[19] following liver and iron in the anemias of pregnacy, chlorosis, hookworm disease and the anemia of undernutrition.[11]

It may be seen, therefore, that the percentage of the reticulated red cells may be increased in various forms of secondary anemias and following different kinds of treatment.

OBSERVATIONS IN FIFTY THREE CASES

The reticulocyte counts of the cases reported in this paper have been summarized briefly in table 1. It may be seen that they varied from

TABLE 1.—*Relationship Between Type of Secondary Anemia and Reticulocyte Response*

Type of Anemia	Cases	Reticulocytes, per Cent
Hookworm	5	5-14
Pregnancy	4	1.4-10
Dysentery (chronic)	7	1.4-28
Undernutrition	5	1.0-15
Chlorosis	3	0.2- 7
Posthemorrhagic anemia	8	1.0-15
Malaria	3	8-35
Splenic anemia	5	4- 8
Anemia following splenectomy	2	5- 8
Kala-azar	6	3- 5.6
Postinfectious anemia	3	0.4- 4.6
Aplastic anemia	1	0- 1.2
Nephritis	1	0- 3

TABLE 2.—*Relationship Between Total Number of Erythrocytes and the Reticulocyte Response*

Total Number of Erythrocytes	Percentage of Reticulocytes
1,000,000 to 1,500,000	0 - 35
1,500,000 to 2,000,000	1 - 13
2,000,000 to 3,000,000	10 or less
3,000,000 to 4,000,000	10 or less
4,000,000 to 5,000,000	7 or less

1 to 35 per cent. The intensity of the increase depended on the severity and the cause of the anemia, and the form of treatment employed during recovery.

The most marked reactions were seen in the anemias associated with hookworm infection, hemorrhage, dysentery, undernutrition, pregnancy and malaria. In the other forms the count varied.

The relationship between the severity of the anemia and the reticulocyte response is recorded in table 2. As a general rule, the

18. Richter, Oscar; Maurer, S., and Eyl, M.: Treatment of Severe Dibothriocephalus Latus Anemia, with a High Caloric Diet, Rich in Liver Extract and Vitamins, J. A. M. A. **91**:1462 (Nov. 10) 1928.

19. Faber, K. F.: Value of Liver Extract (343) in Identifying and in Treating Certain Anemias; Case of Probable Primary Anemia in Infant One and One-Half Months Old, Am. J. Dis. Child. **36**:1121 (Dec.) 1928.

lower the original erythrocyte count, the higher the reticulocyte count may rise during recovery. This was also noted by Minot, Murphy and Stetson [12] following liver therapy in pernicious anemia, and in a few patients with secondary anemia. This reaction varies with the type of anemia and of treatment.

The relationship between the response of the reticulocytes and different forms of therapy in various anemias is summarized in table 3. Besides the fact that the severity and the cause of the anemia influence the reticulocyte response, it seems clear that certain forms of treatment can bring about an increase in the percentage of reticulocytes in some anemias and not in others. For example, the production of reticulocytes in kala-azar does not seem to be influenced by any form of treatment, and the same is true of that in aplastic anemia.

TABLE 3.—*Relationship Between Form of Treatment and Reticulocyte Response*

Type of Anemia	Percentage of Reticulocytes in Spontaneous Recovery	Percentage of Reticulocytes with Various Forms of Treatment				
		Transfusion	Iron	Liver	Liver and Iron	Cod Liver Oil
Hookworm	.....	.....	4-8	5-10	4-14	.....
Pregnancy	.....	1.4-1.6	.....	10	8-10	6-10
Dysentery	4	1-2	4-8	.....	.....	12-28
Undernutrition	.....	.....	10	.....	15	.....
Malaria	8-35	.....	.....	.....	.....	.....
Chlorosis	.....	.....	2-7	3	5.6	.....
Posthemorrhagic anemia	1-4	2-8	1-3	.....	1-15	.....
Splenic anemia	4-8	.....	8	.....	4	4-6
Anemia following splenectomy	4-6	.....	8	.....	.....	.....
Kala-azar	1-5	1.5	1-5	1-5	1-5	1-5
Postinfectious anemia	1-4	.....	1-4	.....	.....	1-4
Aplastic anemia	0.5-1	0.5-1	0.5-1	1	1	1
Nephritis	3	.....	.....	.....	.....	3

The reticulocyte reactions of the various anemias can be discussed in greater detail.

Anemia Associated with Chronic Dysentery.—In the group presenting anemia with chronic dysentery were eight patients. The reticulocyte counts varied from 1.4 per cent to 28 per cent during the period of recovery. In two patients previously reported by Berglund, Keefer and Yang,[8] the improvement followed cod liver oil and a general diet. In others, improvement occurred following transfusion or treatment of the dystentery and a high caloric diet. The anemia in these patients seemed to be related to the state of nutrition. When the patients received an adequate diet, the anemia improved.

Anemia of Pregnancy.—Seyfarth [2] reported that the reticulocytes may be increased over 1 per cent in normal pregnancy. In the anemias of pregnancy, Dameshek [6] distinguished two types according to the reticulocyte response. In one group, the recovery from anemia was like that in pernicious anemia, that is, with an increase in the production

of reticulocytes. In the other, the recovery was like that in the secondary anemias in which recovery takes place without any increase in the production of reticulocytes. Minot, Murphy and Stetson [12] have recorded an increase in the reticulocyte count in the anemias of pregnancy, following liver feeding. Two of our patients recovered following treatment with liver, and the reticulocyte counts were increased.

Posthemorrhagic Anemia.—The reticulocytes may increase to between 30 and 40 per cent in the circulating blood following an acute hemorrhage. This is true in both man and experimental animals. In the chronic posthemorrhagic anemias, the production of reticulocytes may not be increased, and recovery may take place following transfusion or liver and iron without any increase. On the other hand, there are exceptions in which the reticulocytes do increase to 15 or 17 per cent during recovery in this type of anemia following liver and iron.

Anemias of Undernutrition.—The patients who had anemia associated with undernutrition included those in whom the undernutrition was due to a poor and inadequate diet wihout any other demonstrable cause. These patients recovered promptly following treatment with liver and iron and the routine hospital diet.

Chlorosis.—The cases of chlorosis studied occurred in women. The anemia was characterized by a normal number or a slightly reduced number of erythrocytes and a greatly reduced hemoglobin content. No definite cause for the anemia could be discovered, but recovery occurred when iron, or liver and iron, were added to the diet. As a rule, the reticulocytes were not increased above 5 to 7 per cent.

Kala-Azar Anemia.—In our experience, the reticulocytes have never been increased above 6 per cent in any patient with kala-azar and anemia. This is true regardless of the severity of the anemia or any form of treatment.

Aplastic Anemia.—In aplastic anemia, the reticulocytes are constantly low. In the cases recorded by Shen,[20] Dameshek [6] and Seyfarth [2] the counts were never above 4 per cent. In one case the count was never over 1 per cent. This was true regardless of treatment.

Splenic Anemia.—In the group with splenic anemia, we have included the patients with splenomegaly and anemia of unknown cause. We studied three patients before splenectomy and two patients who had become anemic one and five years respectively, following splenectomy. The reticulocytes varied between 4 and 8 per cent in each group. In one patient, iron was effective in producing rapid improvement with an increased reticulocyte count.

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20. Shen, Dorothy: Aplastic Anemias in North China, Nat. M. J. China **14**: 389 (Dec.) 1928.

Anemia of Malaria.—The percentage of reticulocytes may be greatly increased in malaria, as shown by Yang and Berglund,[21] Seyfarth,[2] Davidson and McCrie[22] and others. In the cases we have observed, the counts varied from 8 to 35 per cent prior to specific treatment with quinine.

Postinfectious Anemia.—The recovery of patients from anemia following infections, such as typhus and relapsing fever, was not associated with an increase in the production of reticulocytes. The count varied from 0.4 to 4.6 per cent.

COMMENT

In a previous paper,[11] we pointed out that when both liver and iron were given to some patients with secondary anemia, the regeneration of hemoglobin could be accelerated. This was striking in the anemia associated with hookworm infection, but it was also noted in other forms of secondary anemia. In some instances, the recovery from the anemia occurred in the same way as that from pernicious anemia following liver diet, namely, with an increased number of reticulocytes in the circulating blood. In others, recovery was not accompanied by an increase in number of reticulocytes.

We wish to emphasize the fact that in the case of a number of secondary anemias, patients may recover following treatment with liver and iron, or other forms of therapy and during the period of recovery may show an increase in the percentage of reticulocytes. The intensity of the reaction depends not only on the type of treatment but on the cause and the severity of the anemia. In some cases, the reticulocytes were never increased above 5 per cent regardless of the form of therapy or the severity of the anemia. This was particularly true of the anemia of kala-azar, the postinfection anemias, the aplastic anemias, and of most of the chronic posthemorrhagic anemias. In malaria, the percentage of reticulocytes was generally increased regardless of treatment.

The most striking responses following the various forms of treatment mentioned, were seen in the anemias of hookworm infection, undernutrition, pregnancy and dysentery. In all of these anemias, poor nutrition seemed to play a considerable part. A proper diet supplemented with liver and iron or, in some instances, with cod liver oil, was capable of bringing about an increase in the percentage of reticulocytes and an improvement of the anemia.

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21. Yang, C. S., and Berglund, H.: Difference in Reticulocyte Behavior in Anemia from Malaria and in Pernicious Anemia, Proc. Soc. Exper. Biol. & Med. **26**:417, 1929.

22. Davidson, L. S. P., and McCrie, J. G.: The Phenomenon of Reticulation and Alteration in Size of Red Blood Corpuscle After Liver Therapy, Lancet **2**:1014 (Nov. 17) 1928.

Minot, Murphy and Stetson [12] have recorded a similar reaction following liver diet in some secondary anemias. Two of their cases were associated with pregnancy and the other three with disturbances in nutrition. Bloomfield and Wyckoff [9] have reported favorable results following liver feeding in anemia associated with sprue, and Isaacs, Sturges and Smith [10] and Richter, Maurer and Eyl [15] have recorded the same for anemia due to broad tapeworm.

It would appear from the cases of secondary anemia on which this study is based and the cases previously reported by others that many forms of secondary anemia react in the same way following treatment with liver, or liver and iron, as pernicious anemia reacts following treatment with liver or liver extract. The exact explanation for these observations awaits further study.

SUMMARY AND CONCLUSIONS

In this study of fifty-three cases of secondary anemia, we were able to show that the response of the reticulocytes depends on the severity and the cause of the anemia, and the form of treatment employed during recovery. The highest reticulocyte counts were observed in malaria, anemia due to hookworm, and the anemias associated with dysentery, undernutrition and pregnancy. In the latter four conditions, nutritional disturbances seemed to play a part in the production of anemia, and when the patients with these conditions were treated with liver or liver and iron or cod-liver oil and a high caloric diet, the anemia decreased and the percentage of reticulocytes increased.

In many of the cases of secondary anemia, the results produced in the reticulocyte count by the forms of treatment mentioned were as striking as those seen in pernicious anemia following treatment with liver or liver extract. It would appear, therefore, that feeding of liver as a method of treatment in anemia is not specific for pernicious anemia, but has a beneficial effect in many forms of secondary anemia. In many instances, liver and iron together were more effective than liver or iron alone.

THE ETIOLOGY OF EMPHYSEMA*

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According to Fraenkel,[1] emphysema is found in more than 5 per cent of all autopsies. It is rarely found in children, but increases in frequency with each decade. It is often present in persons about 40 years of age, and frequently occurs during old age. Generally it is described as occurring in three types (excluding interstitial emphysema, which has no relation to the disease under discussion) namely: compensatory, atrophic and hypertrophic or vesicular emphysema.

TYPES OF EMPHYSEMA

Compensatory.—Compensatory emphysema is a condition in which one portion of the lung increases in size and function, when another portion is destroyed or temporarily useless. It occurs, for instance, in association with pneumonias, pleural effusions and pneumothorax. Anatomically, there is found an enlargement of the normal lung; there are no variations from the normal structure; the unaffected lung, as a result of distention, has an increased vital capacity and is able to perform a greater amount of work than when in its usual condition. The tissues show no similarity to those truly emphysematous. This change is in no way related to true emphysema and the term should not be used, as it creates great confusion in the literature. Its use is no more justified than that of speaking of the compensatory enlargement of a kidney, when the opposite kidney has been removed, as of a compensatory nephritis. True emphysema can never compensate for diseased lung tissue, because the emphysematous lung is totally or almost totally functionless.

Atrophic.—The term atrophic emphysema is usually applied to the type of emphysema most commonly found in senility. It is said to be "a part of the atrophic change that occurs everywhere in the body with advancing years. The alveolar walls become atrophic and the lungs lose their elasticity. In contrast to true emphysema, the lungs are small and retracted."[2] Although this statement is found universally in the

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1. Fraenkel, quoted by Staehelin: Handbuch der inneren Medizin, 1914, p. 662. This article and one by the same author in Ergebn. d. inn. Med. u. Kinderh., 1915, p. 516, contain a complete bibliography on emphysema.

2. Hamman, L.: Oxford Medicine, New York, Oxford University Press, 1918, vol. 2, p. 61.

literature, there is no evidence for its truth. The condition does not differ from hypertrophic or vesicular emphysema except in the size of the lungs. This difference may reasonably be attributed to the diminution of function in senility. The size of the lung, like that of every other organ, is known to vary with its use. The lungs of athletes, of users of wind instruments, of glass blowers and even of persons who are dyspneic for reasons fundamentally nonpulmonary are known to be larger than those of persons of sedentary habits or not subject to similar functional disturbances. In senile persons, who are inactive, atrophy of disuse occurs, and even the added emphysematous process may not bring the lungs to a normal size. I see no reason for assuming that the etiologic basis of atrophic emphysema differs from that of the hypertrophic type. Normally, the amount of lung tissue is much greater than is essential for life without marked physical activity. Usually, if lung tissue is destroyed, the remaining lung enlarges. But if normal activity is not resumed, a return to the normal size need not occur. Thus it was possible to remove three lobes of a dog's lung by successive lobectomies without producing dyspnea while the dog remained relatively inactive. Autopsy several weeks after operation presented no compensatory enlargement; the total volume of lung tissue was not much more than half of the normal. Similar conditions might well account for the absence of hypertrophy in association with the emphysema of senility.

Hypertrophic or Vesicular.—In this type of emphysema the lungs are enlarged as a result of an enormous increase in the size of the air vesicles, particularly at the apexes and anterior margins of the lungs. The air spaces may be as large as a hen's egg. They are produced by rupture of the intra-alveolar septums and the merging of many alveoli. It is inconceivable that such spaces can carry on any of the respiratory functions. The capillaries are destroyed, and the passage of air to and from these spaces would be mechanically difficult. Several facts appear to prove that, in at least many cases, these bullae do not communicate with the bronchioles.

Boenninger[3] stated that a pressure of 300 mm. of mercury was insufficient to diminish materially the size of some of these air pockets.

Analysis of the contents of the vesicles proved them to be composed chiefly of nitrogen, the oxygen having been taken from the air originally occupying them (Benecke[4]).

Except for the tissue grossly involved, the structure of the lung appears intact unless other concomitant disease processes are present.

3. Boenninger: Verhandl. d. Kong. f. inn. Med., 26th Congress, Wiesbaden, 1909.

4. Benecke: Verhandl. d. deutsch. path. Gesellsch., 1913, p. 448.

Some have reported the elastic tissue in the alveolar walls as diminished, others as increased. The estimation of the normal amount is so difficult, however, that it is impossible to draw any conclusions from these reports. The tissue involved is naturally inelastic.

Many theories as to the causation of emphysema have been put forth. Some of these appear to be without any foundation. It has been suggested that emphysema is due to a congenital deficiency of the elastic tissue. The only basis for this hypothesis is that the disease has been found in several members of a family. The fundamental defect is believed by some to be an abnormal condition of the wall of the chest.[5] Thus high grades of emphysema have been present in cases of marked kyphosis and scoliosis, and the "barrel chest" of emphysema has been accused of being the cause and not the effect of the pulmonary change. The frequency of emphysema with or without defects in the wall of the chest makes it appear probable that their association is accidental.

In the old textbooks, prolonged or frequently repeated expiratory effort was emphasized as a cause. Glassblowers, blowers of wind instruments, etc., were thought to be commonly affected by emphysema. Both clinical and pathologic evidence have served to discount this factor in the etiology. It has been definitely proved that such effort results in enlargement of the lung, but there is no basis for the further assumption that "if the increased (intra-alveolar) pressure is maintained for a long time, the lung loses its resiliency and a condition in all respects similar to true emphysema occurs."[2] It is also frequently stated that persistent so-called compensatory emphysema changes to the vesicular form. There is no clinical or experimental proof for this belief. Kuhn[6] attempted to produce pulmonary enlargement in dogs by applying masks over their heads. These masks had valves increasing the resistance to expiration. Photographs of his dogs prove an enlargement of the chest, but even after the resistance had been continued for more than a year, apparently nothing suggestive of true emphysema developed in the lungs.

The most generally accepted and most plausible theory as to the pathogenesis of emphysema is that of mechanical obstruction to the air current. From the physical standpoint this would be most likely to result in increased expiratory effort, no matter what might be the nature or the location of the obstructing element. Increased difficulty in inspiration, unless of high grade, is easily overcome by a commensurate increase in the activity of the muscles of the wall of the chest and diaphragm; expiration, on the other hand, being normally a passive

5. Freund, W. A.: Ueber primäre Thoraxanomalien, Berlin, 1906.

6. Kuhn: Die Anwendung der Lungensaugmaske, Therap. Monatschr., 1910, p. 411.

process with relaxation of the musculature, offers greater difficulties. Moreover, the air passages open during inspiration and collapse during expiration, so that any stenosis is exaggerated during the latter.

One might conceive of the effect of an obstruction in the air passages as analogous to that of an enlarged prostate on the bladder. A gradual increase in the residual air in the parts distal to the obstruction might occur, resulting in dilatation of the alveolar spaces. There is little doubt that this actually takes place, but there is no certainty that a true emphysema results. The effect would simulate that of spasmodic expiratory effort, except for its greater intensity and continuity.

If obstruction causes emphysema, the end-result should be the same, no matter what the position of the obstruction. The following are instances of clinical types in which emphysema apparently resulted from obstruction at various levels.

Nasal Obstruction: A man presented himself, complaining of severe dyspnea on slight exertion. On examination, the heart and lungs seemed normal except that the lung volume appeared increased. Roentgen examination gave negative results. The nasal passages were almost completely blocked by polyps. This man was not conscious of the occlusion, was not a mouthbreather even at night and was compelled to increase his respiratory effort to overcome the obstruction. Removal of the polyps resulted in marked diminution of dyspnea and reduction in the size of the lungs.

Laryngeal Obstruction: A young man with cardiac irregularity and physical characteristics of high-grade emphysema was found to have a paralysis of the left vocal cord.

The most extensive emphysema that I have seen occurred in a man whose vocal cords had become agglutinated as a result of tuberculosis to such an extent that only a buttonhole slit remained. The pulmonary tuberculosis was insignificant.

Tracheal Obstruction: A woman, aged 70, with dyspnea, cyanosis and pulmonary enlargement had a large goiter which produced displacement and kinking of the trachea.

At lower levels emphysema is found frequently in cases in which foreign bodies and tumors involve or press on the bronchi.

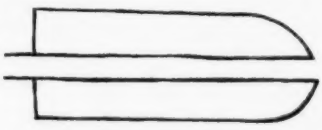
Instances of the types noted lend force to the theory that obstruction of the air passages may produce emphysema. A total occlusion, of course, could not cause distention of the alveoli, but rather an atelectasis. In spite of numerous statements in the literature to the contrary, little experimental work has been done to prove or disprove this theory. Except for the work of Kuhn, I know of none which has any bearing on this problem. Because of the therapeutic possibilities due to the recent great advances in bronchoscopy, it is important to determine the facts of the case. If emphysema is produced by obstruction in the larger air passages, operative removal of the noxious agent would be of prime value in its prevention and treatment. The early recognition should serve to obviate the more advanced forms and, with them, the damage to the circulatory system.

EXPERIMENTAL WORK

Numerous methods were used in attempting to produce obstruction at various levels of the respiratory tracts of dogs. Many technical difficulties were encountered, and the failures are reported for the sake of others engaged in like work.

Narrowing of a Main Bronchus by Ligature or Metal Clamps.—The former invarably resulted fatally, usually after three or four days, either by hemorrhage (cutting through the bronchial artery) or by pneumothorax and pleural infection (cutting through the bronchial wall). When metal clamps were used, the stenosis was only temporary; within a week the clamps could be seen by bronchoscope to lie within the bronchus and the bronchus had resumed its normal contour.

Narrowing of the Trachea by Ligature or by Broad Tape.—No matter what material was used, the result was the same. Within a week, the external pressure had produced atrophy of the tracheal wall and a fistula appeared, which vitiated the experiment.



Brass tubes used in permanent partial tracheal obstruction.

Narrowing of the Larynx by Actual Cautery of the Vocal Cords.—Frequent attempts proved entirely futile. Within a week all of the animals, that survived, had recovered sufficiently to manifest normal functioning of the vocal cords. In none did these present agglutination.

Many efforts were made to produce partial obstruction of the trachea and bronchi by the introduction of foreign bodies of various types into their lumina. Melted paraffin and large molds of paraffin (melting point 50 C.) forced into the bronchi and trachea by way of a bronchoscope were ineffective because they were ejected by the dogs within a few days. Metal cups were also made, perforated at the bottom so as to permit the passage of some air. These could be kept in place only by forcing them into the bronchi as far as possible and attaching to them fine wires, which entered the bronchial mucosa. The openings in these cups, however, soon became closed by mucus, and the obstruction was complete.

A technic for permanent partial tracheal obstruction was finally devised which proved entirely successful. Brass tubes were made as illustrated in the accompanying figure. The diameter of the outer tubes was 18 mm., as nearly as possible equal to the diameter of the trachea of a dog weighing 15 kilograms. The diameter of the inner tubes was

from 4 to 5 mm. so that the area of the duct was less than one-fifteenth of that of the trachea. These tubes were introduced into the trachea by tracheotomy, the curved end toward the body. On account of their size, it was not possible for them to pass through the larynx. The trachea was not sewed, but the fascia and skin were closed loosely, so that any air escaping from the trachea could leave the body instead of being forced into the subcutaneous spaces.

The immediate results of operation were as follows: about two-thirds of the dogs died within twenty-four hours. The cause of death appeared to be a displacement of the tubes upward by coughing; pressure against the vocal cords produced intense tachypnea and death. When tachypnea occurred during periods of observation, the lives of the dogs could be saved by removal of the plugs. In these cases the tubes were too small to fit snugly into the trachea and to be held in situ. Eight dogs survived. Most of these presented an extensive subcutaneous empysema within twenty-four hours, in some instances doubling their original size. This did not appear to incommode them or to affect their health in spite of its grotesqueness. The air, if great in amount, was removed partially by puncturing the back by a trocar. When not so removed, it disappeared spontaneously in from one to two weeks. Cardiac irregularity was noted in each case after the operation; in most instances it disappeared within a few days. In two dogs it persisted for several months. Electrocardiogram of one dog were interpreted as showing sinus arrhythmia, probably due to vagus irritation.

The dogs were examined at least once a week during the period of their survival. The examinations included measurements of the chest, percussion, auscultation and fluoroscopy with and without the use of iodized poppy seed oil—40 per cent. Most of the dogs remained aphonic, but some were able to bark loudly within a few weeks. On exertion, such as running up a flight of stairs, all presented severe dyspnea and became exhausted; some also vomited. While at rest, they appeared normal except that during one hot period, two dogs (the only ones successfully operated at that time) suffered intensely. They became prostrated, had hyperpyrexia (up to 106 F.) and it was felt that they survived only because of frequent bathing. No definite changes were discovered by measurements, percussion or auscultation. Fluoroscopy showed the diaphragm to be somewhat lowered, as indicated by a clear space between the heart shadow and the dome of the diaphragm.

The dogs were killed at intervals of approximately two months. The longest period of observation was fourteen months. Only one died spontaneously. The first dog was killed by a blow on the head by a heavy hammer, the others by bleeding under anesthesia. The former

method was abandoned, because it was found that the lungs contained too much blood for satisfactory sections. During bleeding, tracheotomy was performed, the plug removed and during the last gasps of the dog a diluted solution of formaldehyde, U. S. P. (1:10) was permitted to flow into the trachea from a height not exceeding 50 cm. Artificial respiration was carried on, and the dog was turned in various positions so that the fixative solution might reach all parts of the lungs. A diluted solution of formaldehyde (1:10) was also injected into the abdominal cavity to prevent decomposition. The organs were left to harden in situ for forty-eight hours before dissection; the lungs were then removed and placed in a diluted solution of formaldehyde (1:10) for a week before sectioning.

At autopsy in all cases hypertrophy and dilatation of the right ventricle were present. The trachea at the site of the plug showed atrophy of the cartilage and thickening of the mucosa. Microscopically, there was metaplasia of the mucous membrane. The lining epithelium was squamous in type and consisted of seven or eight layers. On gross examination, the lungs showed no semblance to the vesicular emphysema of the human being. Enlarged alveoli were sometimes seen at the apical margins and in a small lobe lying behind the heart; these were particularly noticeable when examined under low magnification. Microscopically, a few of the alveoli and infundibula in the areas noted appeared dilated, and in a few places the alveolar walls seemed ruptured. These changes were so few and insignificant that one could not feel certain of any pathologic observations in spite of careful study of many sections.

In dogs in which bronchial obstruction had been produced by the introduction of plugs of similar construction, but of smaller caliber, partial obstruction was not obtained because of complete closure of the orifice by mucus.

COMMENT

As a result of these experiments, it appears evident that partial obstruction to respiration alone in dogs is insufficient to produce a condition similar to the vesicular emphysema of man. It is also improbable that emphysema in man can be due to obstruction alone. In spite of the negative results obtained, there is a great amount of clinical evidence pointing to obstruction as an important factor in the pathogenesis of emphysema. It appears, however, that, if so, a concomitant alteration of the finer air passages is essential. Such an alteration occurs in whooping cough and chronic bronchitis, which present both infection and obstruction. In the few areas noted, in which microscopically a picture resembling that of vesicular emphysema was observed, the lining cells of the alveoli were absent and the elastic tissue entirely

denuded. Such a condition would serve to weaken the alveolar walls and result in their destruction.

Further attempts were made to test the validity of this assumption. Irritants of several types were introduced into the lungs via the bronchoscope, simultaneously to produce obstruction and inflammation. Among others, powdered talcum, barium and bismuth salts and iron powder were used. Unfortunately, even the heavy powders were expelled rapidly, judging by fluoroscopy, within a few hours. The dog reacts unfavorably to pulmonary infections, and the addition of this factor to obstruction does not promise satisfactory experimental results.

Many bronchoscopists have reported the existence of bronchiectasis in cases of partial obstruction of a bronchus by a foreign body with infection of the bronchus below.[7] A similar association in the bronchioles and infundibula might well be responsible for dilatation of the finer air spaces. It is true that at autopsy emphysema may be found without concurrent infection. This does not prove, however, that an infection was not present when the emphysema developed. If, as is generally believed, whooping cough gives rise to emphysema, the latter would persist after the infection of the bronchioles had disappeared. Similarly, other infections might be overcome, but there is no possibility of a restitutio ad integrum following emphysema. The fact that emphysema is frequently a terminated process and not progressive in character is indicated by the fact that in the vast majority of cases found at autopsy the disease has been entirely unsuspected, and not even careful scrutiny of the history presents symptoms suggestive of emphysema.

CONCLUSIONS

1. Long continued high-grade obstruction of the air passages of dogs was insufficient to produce a pathologic picture simulating vesicular emphysema in man.

2. If obstruction is a factor, an additional factor or factors, as an associated infection of the finer respiratory passages is an essential concomitant. It is possible, but improbable that an expiratory obstruction much greater than inspiratory might be adequate.

NOTE.—While this paper was in press, my attention was called to an article by W. H. Harris and F. P. Chillingworth (The Experimental Production in Dogs of Emphysema with Associated Asthmatic Syndrome by Means of an Intratracheal Valve, J. Exper. Med. **30**:75, 1919). The technic employed was almost identical with that described. The presence of a gutta percha ball acting as a valve to increase the expiratory difficulty should make little change in the resulting pathologic condition. Their dogs were kept for periods of from one day to three weeks. In some of these animals (number not stated) infection played a

7. Many papers from the Clinic of Chevalier Jackson. Myerson, M. C.: Benign Neoplasms of Bronchus, Am. J. M. Sc. **176**:720, 1928.

rôle as evidenced by the presence of lobular pneumonia. Their conclusions were that the production of emphysema was found to vary in extent and degree according to the type of valve employed and the duration of the experiment. My first impression also was that I had succeeded in producing emphysema, but I discovered that there were no greater changes after fourteen months than in the shorter experiments. They also stated that in control animals and "in a considerable proportion of dogs employed in routine physiological laboratory work" slight emphysema was noted on the edges of the lung. In all dogs examined, operated and control, the alveoli and infundibula at the margin were much larger than those found elsewhere, and they were therefore considered as normal, not emphysematous. The photomicrographs and photographs of the gross lung illustrating their article were practically identical with my observations, but I did not interpret these changes (the pneumonia excepted) as pathologic, and several pathologists who were consulted did not believe them to be emphysematous. In brief, their technic and results were practically identical with mine, but the conclusion that tracheal obstruction (without infection) resulted in emphysema does not agree with that reached by me.

AMYLASE IN THE BLOOD IN SUBACUTE AND IN CHRONIC PANCREATIC DISEASES *

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Since 1833, when Payen and Persoz [1] precipitated a starch-splitting substance from malt and gave it the name of diastase, the so-called diastatic activity of blood and of the various excreta from man and animals has been widely studied in health and in disease. The diastatic activity of the blood was observed first by Magendie [2] who showed that the blood was capable of splitting starch into sugars. In general, not much advancement was made, in spite of the methods offered from time to time, until Wohlgemuth [3] described a quantitative method for determinations of amylase in 1908. Following Wohlgemuth's work, various quantitative methods were described which depended on the ability of amylase to effect a given change in a known solution of starch. Results obtained by these methods led such authorities as Van Slyke and Cullen [4] to think that, in general, enzymes obey the law of mass action and that apparent divergences from this law are due to secondary reactions. It has been objected that enzymes do not obey the law of mass action because they are colloidal solutions. There is evidence, however, to show that this may not be so. Northrop,[5] for instance, contended that it is reasonable to assume that colloidal solutions are governed by the law of mass action because it can be shown that colloidal solutions obey the law of gases and the laws of thermodynamics from

* Submitted for publication, Aug. 5, 1929.

* From the Division of Medicine, the Mayo Clinic.

1. Payen and Persoz: Mémoire sur la diastase, les principaux produits de ses réactions et leurs applications aux arts industriels, Ann. chim. & phys. **53**:73, 1833.

2. Magendie: Note sur la présence normale du sucre dans le sang, Gaz. méd. de Par. **1**:734, 1846.

3. Wohlgemuth, J.: Ueber eine neue Methode zur Quantitativen Bestimmung des diastatischen Ferments, Biochem. Ztschr. **9**:1, 1908.

4. Van Slyke, D. D., and Cullen, G. E.: The Mode of Action of Urease and of Enzymes in General, J. Biol. Chem. **19**:141, 1914; **28**:391, 1916-1917.

5. Northrop, J. H.: I. The Inactivation of Trypsin, J. Gen. Physiol. **4**:227 (Jan.) 1921-1922. II. The Equilibrium Between Trypsin and the Inhibiting Substance Formed by Its Action on Proteins, J. Gen. Physiol. **4**:245 (Jan.) 1921-1922.

which the law of mass action may be derived. Furthermore, Northrop has confirmed his contention by experimental observation.

Northrop and Hussey [6] conceived the idea of measuring the viscosity of solutions containing enzymes during the period of action of the enzymes. This they did by using a 3 per cent solution of gelatin during tryptic digestion. They found that the time required to effect a given change in the initial viscosity of the substrate was inversely proportional to the amount of the enzyme employed (Arrhenius' rule of QXT).

Davison [7] employed the technic used by Northrop and Hussey to determine diastatic activity, using a boiled, autoclaved, buffered solution of starch two and a half times more viscous than water and obtained for diastase results similar to those which were obtained by Northrop and Hussey for trypsin and pepsin. Maslow and Davison [8] compared the viscosimetric with other accepted methods for determination of the activity of diastase, and found that the results checked fairly well. O'Donovan and Davison,[9] using the viscosimetric method, could show the presence in the blood of the normal amylase-accelerator.

The viscosimetric method apparently has advantages over methods that preceded it in that it allows of objective control of more conditions during the determination. The technic used in our work was that advocated by Elman and McCaughan.[10]

Our object was to determine whether, in patients with known or suspected pancreatic disease, we could detect changes in the concentrations of amylase in the blood which might be of diagnostic significance. Elman and McCaughan observed that the amylase in the blood of normal animals was comparatively uniform in amount. In animals with experimentally produced obstruction of the pancreatic ducts, the amylase rose, within a few days, to high levels and then gradually fell. This observation had been made before.

We observed patients who were in the hospital for known or suspected pancreatic disease. In order to check the results being

6. Northrop, J. H., and Hussey, R. G.: A Method for the Quantitative Determination of Trypsin and Pepsin, J. Gen. Physiol. **5**:353 (Jan.) 1922-1923.

7. Davison, W. C.: A Viscometric Method for the Quantitative Determination of Amylase, Bull. Johns Hopkins Hosp. **37**:281, 1925.

8. Maslow, E. L., and Davison, W. C.: A Comparison of the Viscometric Copper Reduction, Polariscopic, and Iodometric Methods for Measuring the Rate of Hydrolysis of Starch and Dextrin by Aspergillus Oryzae, J. Biol. Chem. **68**:75 (April) 1926.

9. O'Donovan, Charles, Jr., and Davison, W. C.: The Amylase-Accelerator and Anti-Trypsin of Normal Human Serum, Bull. Johns Hopkins Hosp. **40**:238, 1927.

10. Elman, Robert; and McCaughan, J. M.: The Quantitative Determination of Blood Amylase with the Viscosimeter, Arch. Int. Med. **40**:58 (July) 1927.

obtained, from time to time determinations were made on patients without suspected pancreatic disease or on normal subjects. Values for amylase in five normal subjects were respectively 4.2, 6.0, 7.0, 5.1 and 7.2. The values for amylase are expressed in units that indicate a quantity of amylase that will effect, in one hour, a change of 20 per cent

TABLE 1.—*Amount of Amylase in Blood in Pancreatic Diseases*

Case	Age, Yrs.	Sex*	Diagnosis	Symptoms	Amylase, Units
1	44	♂	Subacute cholecystitis, cholelithiasis, hemorrhagic pancreatic cyst, fat necrosis	Symptoms of peptic ulcer for fifteen years; ruptured duodenal ulcer, three months previously; pneumonia; nausea for six weeks; no pain	15.1
2	61	♂	Obstructive jaundice, carcinoma of pancreas	Epigastric distress for three months; painless jaundice for ten days	5.6
3	45	♂	Obstructive jaundice, carcinoma of pancreas	Painless jaundice for six weeks.....	5.1
4	41	♂	Obstructive jaundice, carcinoma of pancreas	Painless jaundice for seven weeks.....	7.1
5	55	♂	Obstructive jaundice, carcinoma of pancreas	Weakness for four months; chills and fever for two months; jaundice for ten days	75.0
6	63	♀	Obstructive jaundice, carcinoma of pancreas with metastasis to liver	Nausea for two weeks; jaundice for one week	4.2
7	43	♀	Obstructive jaundice, carcinoma of pancreas	Painless jaundice for four months; severe pruritus for five weeks	3.2
8	64	♂	Obstructive jaundice, carcinoma of pancreas	Painless jaundice two years previously; cholecystduodenostomy twenty-two months previously	3.5
9	72	♀	Obstructive jaundice, carcinoma of pancreas	Indigestion one year; diarrhea three months; painless jaundice one month	1.7
10	49	♂	Obstructive jaundice, carcinoma of pancreas	Painless jaundice six weeks.....	3.2
11	43	♂	Obstructive jaundice, carcinoma of pancreas	Onset of jaundice with epigastric pain seven months previously; jaundice with only occasionally some epigastric pain for six months	3.2
12	60	♂	Obstructive jaundice, carcinoma of pancreas	Painless jaundice for five weeks; chills and fever for four weeks	4.0
13	46	♂	Stone in common bile duct, pancreatitis, enlargement and induration of head of pancreas and surrounding tissue	Chills for four months; fever and glycosuria at times	4.6
14	38	♂	Carcinoma at ampulla of Vater, obstructive jaundice	Painless jaundice for three and a half months; pruritus for three months	38.0
15	72	♂	Obstructive jaundice, carcinoma of pancreas	Painless jaundice for two months; pruritus for six weeks	3.8
16	55	♂	Obstructive jaundice, carcinoma of pancreas	Painless jaundice for six weeks; diarrhea for three weeks	8.0
17	64	♂	Obstructive jaundice, carcinoma of pancreas	Painless jaundice for seven weeks; severe pruritus for six weeks	5.0
18	45	♀	Cyst in pancreas.....	Severe epigastric pain for seven months, collapse, shock, in bed for three months	53.0
19	52	♀	Obstructive jaundice, carcinoma of pancreas	Jaundice for five weeks; pruritus for four weeks	12.3
20	47	♀	Obstructive jaundice, carcinoma of pancreas	Jaundice for eighteen months; pruritus and diarrhea for fifteen months	3.5

* In this column, ♂ stands for male; ♀, female.

in the viscosity of 5 cc. of a 7 per cent buffered solution of starch. Special preparations were not made. Blood for determinations of amylase was drawn at any convenient time during the day, as it has been shown that values for amylase in blood are remarkably constant and apparently are not influenced by intake of food.

In table 1 are shown the results of determinations on twenty patients with known pancreatic disease. The age and sex did not have any

relation to the results. The clinical and surgical diagnoses usually agreed, but in table 1 the condition found at the time of operation is given. A note as to the duration and nature of the disease is included. In cases 1, 5, 14, 18 and 19, the amounts of amylase are definitely increased (normal values are from about 4 to 8 units). In these five cases there is nothing in the case histories or in the records of surgical examination that is particularly significant or different from other cases, except in case 18. In this case, the illness of the patient, a woman, dated from an acute attack of pain in the upper part of the abdomen which was followed immediately by collapse; this had occurred six

TABLE 2.—*Amount of Blood Amylase in Various Diseases*

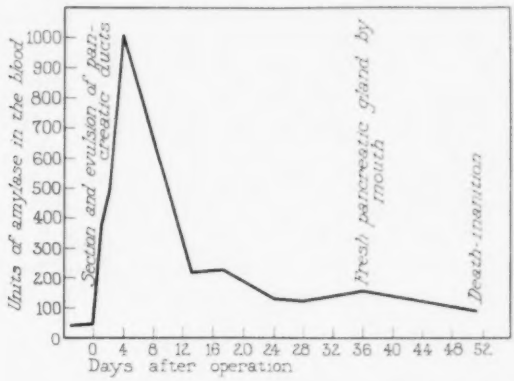
Case	Diagnosis	Amylase, Units
1	Obesity, psychoneurosis, migraine	8.5
2	Chronic infectious arthritis	4.2
3	Catarrhal jaundice	2.6
4	Diabetes mellitus, dwarfism	15.7
5	Diabetes mellitus, catarrhal jaundice	5.9
6	Diabetes mellitus, obesity	4.0
7	Obstructive jaundice, stone in common bile duct	3.9
8	Adenomatous goiter, hyperthyroidism, catarrhal jaundice	3.7
9	Diabetes mellitus, chronic cholecystitis, obesity	3.4
10	Chronic diffuse nephritis, hypertension, myocardial failure	4.8
11	Catarrhal jaundice	5.6
12	Biliary cirrhosis, splenomegaly	3.2
13	Obstructive jaundice, cholecystitis with stones	3.3
14	Diabetes mellitus, obstructive jaundice, stone in common bile duct	3.5
15	Diabetes mellitus, cholecystitis with stones	3.3
16	Obstructive jaundice, stone in common bile duct	4.1
17	Cirrhosis of the liver, stricture of common bile duct	3.1
18	Chronic nervous exhaustion, mucous colitis	6.2
19	Diabetes mellitus, pituitary tumor (acromegaly), latent syphilis	21.0
20	Carcinoma of stomach with pyloric obstruction	1.3
21	Hypoglycemia	3.0
22	Essential arterial hypertension, vasomotor instability, neurosis, erythromelalgia, transient glycosuria	1.8
23	Chronic nervous exhaustion	4.6
24	Obstructive jaundice, stricture of the common bile duct	3.4
25	Pott's disease, diabetes mellitus	1.8
26	Carcinoma of stomach	3.5
27	Duodenal ulcer	4.6
28	Obstructive jaundice, stone in common bile duct	4.1
29	Chronic nervous exhaustion	3.2
30	Duodenal ulcer	2.8

months before she had come to the clinic. She had improved slowly after the pain and collapse, but had been confined to her bed practically all the time since then. She had had some epigastric pain, but the main feature of her illness was weakness, with progressive abdominal enlargement. At operation, a large pancreatic cyst was found and drained.

Table 2 shows the results obtained in thirty patients with various diseases, many of whom had diabetes mellitus. The only two patients in this group with elevated amounts of amylase were a dwarf (case 4), and a patient with acromegalia (case 19), both of whom had diabetes mellitus. The patient with acromegalia died in the hospital, and at necropsy a pituitary tumor was found. Nothing remarkable was found in the pancreas.

COMMENT

In general, the results of our studies were similar to those obtained by Elman.[11] He reported determinations of amylase on thirty patients without pancreatic disease. His results were fairly uniform. In two cases of pancreatic cysts and one of acute pancreatitis, values for amylase in the blood were elevated. In our series of twenty patients with known pancreatic tumor, there were two with pancreatic cysts, and in both the values for amylase in the blood were elevated. In only four of the twenty were there increased amounts of amylase. Elman has reported one case of carcinoma of the pancreas with a value for amylase in the blood of 0.5 unit. We did not observe a value as low in any patient. In case 8 (table 1) carcinoma of the pancreas had been present for more than two years.



Amylase in blood of experimental animal.

The increase in the amount of amylase in the blood of the two patients represented in table 2 brought up the question as to the source of the amylase. It is found in a number of tissues in the body other than the pancreas and salivary glands. In 1913 Macleod[12] showed, however, that the amount of diastase was greater in the blood than in other organs and concluded that the gradient of pressure was from the pancreas to the blood. Elman and McCaughan did not observe variations in the amount of amylase in the blood after several days of total drainage to the outside of the pancreatic juice. This is taken to indicate that intestinal absorption of amylase does not play a demonstrable part in maintaining the normal levels of amylase in the blood.

11. Elman, Robert: The Blood Amylase in Pancreatic Disease, Proc. Soc. Exper. Biol. & Med. **25**:173, 1927-1928.

12. Macleod, J. J. R.: Diabetes: Its Pathological Physiology, London, E. Arnold, 1913, p. 151.

Not enough is known about the origin and physiologic function of diastase to attempt explanation of increases or decreases of the amount of amylase in the blood in health. Under abnormal conditions, such as complete obstruction of the pancreatic duct produced by ligation, the amylase in the blood is definitely increased. This increase is of definite duration in the experimental animal, and is much higher than that which has been observed under any other circumstances. One of us (McCaughan) obtained the data shown in the accompanying chart. The major and minor pancreatic ducts of a dog were sectioned and evulsed. The possibility of the existence of accessory ducts was excluded by careful search. On the fifty-first day after operation, the animal died. Postmortem examination did not disclose any other cause for death than the inanition incident to the complete loss of pancreatic digestion. The reading obtained just prior to death was about double that of the preoperative level. This suggests that the value of the study of blood amylase as a diagnostic test in pancreatic disease is limited by two factors: The estimations must be made within a comparatively short time after the occurrence of obstruction of the ducts, and the obstruction must be of sufficient degree that absorption of the amylase by the blood stream will yield values far enough beyond the normal range to be of definite significance. It is also suggested that values much below the normal may occur when complete atrophy of the gland follows long continued total obstruction; naturally, the declining curve may at some time or other again fall within the normal range, thus rendering proper interpretation difficult or impossible.

SUMMARY AND CONCLUSIONS

In a group of twenty patients known to have pancreatic tumors, the values for amylase in the blood were increased in six and normal in fourteen.

In a group of thirty patients suffering from various diseases, the values for amylase in the blood were increased in two.

Blood amylase values were found increased in two patients, with anomalies of growth, namely, dwarfism and acromegalia. This suggests a possible relationship between increased blood amylase values and pituitary dysfunction.

Although the series of clinical cases studied is small, it seems probable that the percentage of positive data in pancreatic disease would be similar in a larger series. The percentage is too small to warrant the adoption of a routine diagnostic procedure of study of the amylase of the blood in cases of suspected pancreatic disease.

Book Reviews

TULAREMIA. HISTORY, PATHOLOGY, DIAGNOSIS AND TREATMENT. By WALTER M. SIMPSON, M.S., M.D., Director of the Diagnostic Laboratory, Miami Valley Hospital, Dayton, Ohio. Foreword by Edward Francis, Surgeon U. S. Public Health Service. Price, $5. New York: Paul B. Hoeber.

It is fitting that information on this widespread new disease should be collected and published in book form. The author calls attention to the service rendered by the United States Public Health Service in discovering and accurately determining the sources of infection and the means of diagnosing this disease. Fifteen Public Health Service laboratory workers have contracted tularemia. The earliest written description of tularemia in man appears in a letter written in 1904 by a boy of 15 years to his sister, describing an illness which he attributed to contact with rabbits.

During at least thirty years meat handlers had recognized the characteristic lesion of tularemia which they called "rabbit fever." He describes the tireless work of Dr. Edward Francis in studying the various sources of infection. This historical chapter furnishes most interesting reading.

A chapter is devoted to the zoologic distribution of tularemia, with a long list of mammals and insects that may act as carriers of the infection.

Chapter 5 is devoted to the clinical manifestation of tularemia, including its distribution. Cases have now been reported from every state except the states in New England, Delaware and Washington, with Ohio holding first place, almost certainly due to the efforts of the author. The various clinical manifestations of the disease are described clearly and are illustrated profusely with excellent photographic reproductions.

Chapter 6 is devoted to the pathology of tularemia. Here, as in the preceding chapter, a clear text is further elucidated by suitable illustrations.

Chapter 7 is given over to the bacteriology of tularemia.

Chapter 8 presents in an interesting manner the serology of tularemia. Agglutination which reaches its maximum during the third week shows a high titer, 1:1,280 or 1:256. Agglutination still occurs in a lower titer after the lapse of twenty years.

The final chapter is devoted to treatment, followed by an extensive bibliography.

The style in which this book is written makes it fascinating reading. The print is large and the illustrations are good. The reviewer has much to commend and nothing to criticize.

MEDIZINISCHE PRAXIS. Sammlung für Arztliche Forbildung. Volume VII. Der Sogenannte Rheumatismus. By DR. JULIUS BAUER, Professor at the University of Vienna. Price, 10.50 Rm. Dresden: Theodor Steinkopff, 1929.

The object of this series of monographs is to furnish practical information to the physician. This volume contains little that is new and is of limited value as an aid to acquiring knowledge of this little understood disease.

The author discusses acute arthritis, chronic arthritis, myalgia and neuralgia. Myalgia and neuralgia are discussed as conditions distinct from chronic arthritis. It is highly probable that neuralgia is a root pain secondary to spinal osteo-arthritis. In discussing chronic arthritis, instead of using the expression atrophic arthritis or rheumatoid arthritis, he uses the term chronic polyarthritis — considering the process an inflammatory one. This is in accord with the prevailing view in this country. He considers osteo-arthritis a disease of years, as each decade after twenty years shows an increasing frequency. In this he is in accord

with the widely accepted belief in this country that the disease is a degenerative rather than an infectious process.

The illustrations are good, and there is a limited bibliography.

DIET AND EFFICIENCY. A FIVE-YEAR CONTROLLED EXPERIMENT ON MAN. By HAROLD H. G. HOLCK. Price, $1.00. Chicago: University of Chicago Press.

Experimental studies such as this are all too rare in the field of dietetics. As Carlson says in the preface, "Scientific knowledge of the relation of the diet to health and efficiency . . . has played little or no rôle in human evolution." Fads have been followed as facts; newspaper and propagandist information has been accepted as truth. The experimental method applied to food and human life is difficult, but the present study seems to have overcome the major difficulties, and therefore the conclusions are of value. The problem was to study the effect of modified "fletcherizing" of food; the technic and the standards were carefully controlled. The accumulated data are too detailed to review, but the summary of results indicates that "fletcherizing" decreased muscular endurance, typewriting accuracy and basal metabolism, and that it had no effect on blood pressure, pulse rate, oral temperature, sleeping time, mental multiplication and typewriting speed. Improvement in efficiency in solving chess problems was noted, and the rather high body weight was lowered to a more nearly normal standard.

OUTLINE OF PREVENTIVE MEDICINE FOR MEDICAL PRACTITIONERS AND STUDENTS. Prepared under the auspices of the Committee on Public Health Relations of the New York Academy of Medicine. Cloth. Price, $5. Pp. 398. New York: Paul B. Hoeber, Inc., 1929.

This is a medium sized, flexible leather bound volume, consisting of twenty-one chapters and an index, each chapter of which has been contributed by a well qualified specialist. It was prepared particularly for use by general practitioners and students of medicine, whose "usual attitude toward preventive medicine is, of course, commendatory but not exactly enthusiastic"; also, it has been written primarily to arouse their interest in preventive medicine and periodic health examinations, thereby meeting a demand which the public has been educated to make. Closer cooperation by the general practitioner and specialist with health boards, school authorities, community social agencies, etc., is stressed.

Well written, avoiding technical terms and carefully compilated, it fills a distinct need and should prove a useful guide.

RHEUMAPROBLEME, GESAMMELTE VORTRÄGE. By VARIOUS AUTHORS. Price, 12 marks. Pp. 181, with 55 illustrations including 4 colored plates. Leipzig: Georg Thieme, 1929.

This volume contains the initial series of lectures that were delivered at the Rheuma-Forschungs-Institut am Landesbad der Rheinprovinz in Aachen, Oct. 18-20, 1928. Chronic arthritis, muscular rheumatism and rheumatic fever all are dealt with from the pathologic, clinical and therapeutic points of view. Most of the chapters contain admirable summaries of the present knowledge and ignorance of the particular field discussed. The chapter by Fritz Gudzent on the chronic arthritides is especially to be recommended for its conservatism and conciseness. Hugo Schottmüller's contribution on rheumatic fever is excellent.